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## **Ethics Advisory Board**

Department of Health,  
Education, and Welfare

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Appendix:

### **HEW Support of Research Involving Human *In Vitro* Fertilization and Embryo Transfer**

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# **Ethics Advisory Board**

Department of Health,  
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Appendix:

## **HEW Support of Research Involving Human In Vitro Fertilization and Embryo Transfer**

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I

ETHICAL ISSUES





ETHICAL ISSUES IN HUMAN IN VITRO FERTILIZATION  
AND RESEARCH INVOLVING EARLY HUMAN EMBRYOS

LeRoy Walters, Ph.D.





ETHICAL ISSUES IN HUMAN IN VITRO FERTILIZATION  
AND RESEARCH INVOLVING EARLY HUMAN EMBRYOS

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## Ethical Issues in Human In Vitro Fertilization

### and Research Involving Early Human Embryos

The aim of this paper is to provide a survey of ethical issues raised by human in vitro fertilization and related research techniques. The paper is divided into two parts, the first devoted to human research already in progress or currently being proposed, the second to potential future areas of research. Each of these parts, in turn, is divided into two sections which discuss the rather distinct issues arising in the basic-research context and the clinical-research context.

The analysis which follows is intended to complement the fetal-research report of the National Commission for the Protection of Human Subjects.<sup>1</sup>

In the Commission's report "fetus" was defined as

...the human from the time of implantation until a determination is made following delivery that it is viable or possibly viable. If it is viable or possibly viable, it is thereupon designated an infant.<sup>2</sup>

The present paper focuses on early human embryos (here defined as human embryos from the zygote through the blastocyst stages<sup>3</sup>) and on later human embryos or fetuses which are never implanted in the human uterus.<sup>4</sup>

Although this paper is focused on ethical issues rather than on biological data, a brief sketch of the major stages in embryonic and fetal development may serve to make the following ethical discussion more concrete. Fertilization creates a one-celled zygote which, after 24 to 36 hours, begins to divide. No special name is assigned to the 2-, 4-, and 8-cell human embryo. However, at about the 16-cell stage, the embryo

resembles a "little mulberry" and is therefore called a morula. At about the 50- or 60-cell stage, a fluid-filled cavity begins to appear in the embryo, thus marking the transition from the morula to the blastocyst (blastos = germ; kystis = bag) stage. At one side of this cavity a group of cells (called the embryoblast) gradually becomes visible. A diagrammatic representation of these stages in early embryonic development follows<sup>5</sup>:

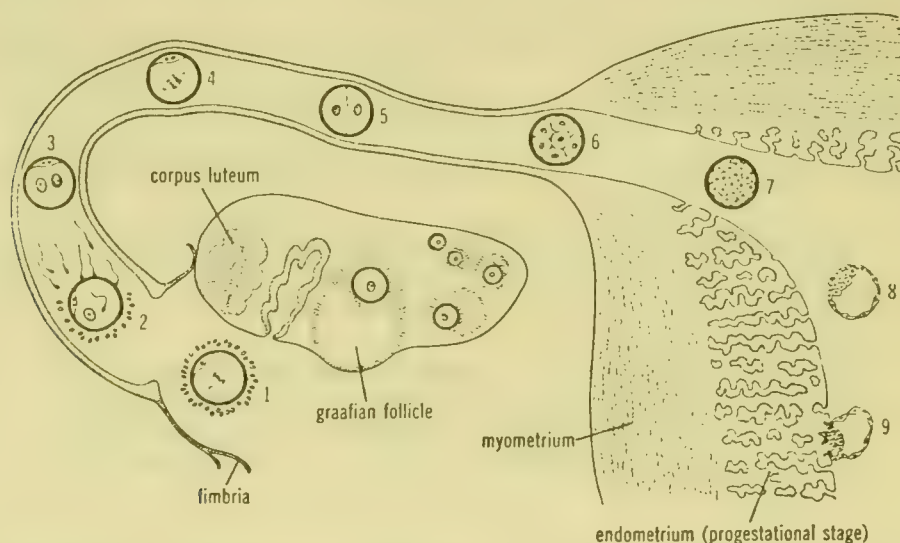


Figure 2-5. Schematic representation of the events taking place during the first week of human development. (1) Oocyte immediately after ovulation. (2) Fertilization approximately 12 to 24 hours after ovulation. (3) Stage of the male and female pronuclei. (4) Spindle of the first mitotic division. (5) Two-cell stage (approximately 30 hours of age). (6) Morula containing 12 to 16 blastomeres (approximately 3 days of age). (7) Advanced morula stage reaching the uterine lumen (approximately 4 days of age). (8) Early blastocyst stage (approximately 4½ days of age). The zona pellucida has now disappeared. (9) Early phase of implantation (blastocyst approximately 6 days of age). The ovary shows the stages of the transformation between a primary follicle and a Graafian follicle as well as a corpus luteum. The uterine endometrium is depicted in the progestational stage.

The mature human blastocyst, approximately 120 to 140 hours old and consisting of approximately 110 cells, can under appropriate conditions implant in the maternal uterus.<sup>6</sup>

Following implantation, the human embryo or fetus normally undergoes the following changes at the gestational ages noted:



Commencement of heartbeat (beginning of 4th week)  
 Cerebral ventricles distinct (end of 5th week)  
 Name changes from embryo to fetus (beginning of 9th week)  
 Sex differentiation (8th to 10th week)  
 Usual occurrence of "quickening" (17th to 20th week)  
 Viability (24th to 26th week in some cases)  
 Birth (38th week in many cases).<sup>7</sup>

## I. Immediate Issues

Since the ethical issues in basic research on human in vitro fertilization (hereafter abbreviated IVF) are somewhat simpler than those involved in clinical applications of the technique, a case could be made for discussing basic research first, then proceeding to the more complex topic. However, the ethical literature on IVF is predominantly devoted to the analysis of issues in clinical applications of IVF; by volume, perhaps eighty to ninety percent of the literature considers clinical questions. Therefore, the following review begins with a discussion of ethical issues in clinical research involving IVF before turning to a consideration of ethical issues in basic IVF research.

### A. Clinical Research

A variety of issues have been raised by commentators on the ethics of clinical IVF research. In descending order of prevalence in the ethical literature,<sup>8</sup> these issues are the following:

1. Risks of clinical IVF research to the potential product of IVF
2. The moral status of the early embryo
3. The need for clinical IVF research
4. Potential long-term social consequences of clinical IVF research
5. The need for and adequacy of prior laboratory research, including animal research, on embryo transfer
6. Informed consent by participants in clinical IVF research
7. Potential psychosocial complications resulting from the donation and receipt of sperm, oocytes, or embryos
8. Risks of clinical IVF research to the oocyte donor

9. The naturalness or artificiality of laboratory-assisted methods of reproduction like IVF
10. Appropriate institutional frameworks for the provision of advice on or monitoring of clinical IVF research
11. Liability or compensation for IVF research-related injuries
12. Appropriate allocation of research and clinical resources to clinical IVF research and to other areas of research or health care

The arrangement of these rather diverse topics into a coherent framework presents a challenge to the would-be reviewer. What follows is merely one way of organizing the material. Two of the topics (nos. 2 and 9) seem clearly to concern presuppositions of the IVF discussion. Several additional topics are specific instances of general ethical issues in research involving human subjects (nos. 1, 3, 5, 6, 8, and 11). In contrast to these six topics, which focus on the rights and responsibilities of individual research subjects and clinical investigators, there are three other topics (nos. 4, 10, and 12) which relate to broader social dimensions of clinical IVF research -- either its potential social consequences or social policy judgments which will need to be made regarding the research. Issue no. 7 -- the donation of sperm, oocytes, or embryos -- will be discussed as a special case.

In summary, the outline for this section of the paper will be as follows:

1. Presuppositions
  - a. The moral status of the early embryo
  - b. The naturalness or artificiality of laboratory-assisted methods of reproduction
2. Ethical issues related primarily to individual research subjects
  - a. The need for clinical IVF research
  - b. The need for and adequacy of prior laboratory research, including animal research, on IVF and embryo transfer
  - c. Risks of clinical IVF research to the potential product of IVF
  - d. Risks of clinical IVF research to the oocyte donor
  - e. Informed consent by participants in clinical IVF research
  - f. Liability or compensation for IVF-research-related injury



3. Broader social and public policy issues
  - a. Potential long-term social consequences of clinical IVF research
  - b. Appropriate allocation of research and clinical resources to clinical IVF research and to other areas of research or health care
  - c. Appropriate institutional frameworks for the provision of advice on or monitoring of clinical IVF research
4. Special case: potential psychosocial complications resulting from the donation and receipt of sperm, oocytes, or embryos.

As the foregoing outline implies, clinical IVF research involving only the gametes of an established heterosexual couple will be discussed as the simplest paradigm case. The additional complexities potentially entailed in the donation of sperm, oocytes, or embryos will be considered separately.

1. Presuppositions

- a. The moral status of the early embryo. In the clinical research context the primary issue, given the current state of the art, is the morality of discarding untransferred early embryos. Ethical issues in research on untransferred embryos will be discussed in the section of this review devoted to basic research issues. In vitro culture of human embryos beyond the blastocyst stages has not yet been reported in the scientific literature.

Two major views on the status of the embryo can be identified. Several commentators argue that the early embryo either is or may be protectable humanity. Leon Kass, who in 1971 admitted uncertainty regarding the moral status of early embryos, advanced several arguments for their potential protectability: (1) the embryos are "biologically alive"; (2) "there is a continuity of development" between earlier and later stages of embryonic and fetal life; and (3) embryos produced in the clinical IVF context are not the result of reproductive accidents, nor does their existence conflict with the rights of any woman; rather, they are deliberately created.<sup>9</sup> In

a recent essay André Hellegers and Richard McCormick note that embryo loss is not confined to the discard procedure but includes as well the loss of about 200 transferred embryos in the research efforts of Edwards and Steptoe alone prior to their success with Mrs. Brown. The authors continue:

Are these really mini-abortions? The evaluation of nascent life in these early days is indeed a problem. But that does not mean the problem can be decreed out of existence by simply going ahead. Where human life is at stake and we have doubts about its evaluation, does not prudence dictate that as a general rule life enjoy the benefit of our doubts?<sup>10</sup>

While bracketing the discard-argument in his own ethical analysis of IVF, Paul Ramsey observes that

Persons who believe that an individual human life begins with conception or after the time of segmentation, or at implantation, or with the morphologically human fetus, or with heartbeat or ECG readings, or self-movement (or any other time before birth) must regard experiments in vitro fertilization as ab initio inherently immoral, because the physician must be willing to discard mishaps at any point in that span of time which do not come up to the standards of an acceptable human being.<sup>11</sup>

In their survey of ethical issues in artificial fertilization, Alun F. Jones and Walter F. Bodmer present both the arguments for and the arguments against the protectability of early human embryos without explicitly adopting either view.<sup>12</sup>

Other commentators who have considered the moral status of the early embryo in clinical IVF research have concluded that the embryo is not a human subject in the moral sense. R. G. Edwards presents perhaps the most extensive brief for the non-protectability position. Edwards adduces the following arguments: (1) "fertilization is only incidental to the beginning of life," since "processes essential to development begin long before ovulation,

and parthenogenic fetuses can develop partially, and perhaps one day wholly through gestation"; (2) nuclear transfer experiments demonstrate that "all nuclei can potentially sustain the development of an embryo"; (3) many persons implicitly accept the abortion of early embryos since "IUD's almost certainly expel unimplanted embryos from the uterus"; and (4) "the gradual acquisition of human rights during development is... clearly illustrated by the prevalence of eugenic abortion, but not infanticide, in cases of inherited anomalies."<sup>13</sup> Joseph Fletcher also rejects the view that prenatal life at any stage is "human in the sense of a person, a 'human being' or a 'nascent' human being, with a 'right to life'".<sup>14</sup> Impressed by the estimated fifty percent embryonic loss rate during the first two weeks of in vivo human reproduction and by the possibility of twinning during the same time period, moral theologian George Lobo argues that the death of early embryos in clinical IVF research precedes "homini-zation" and is therefore morally acceptable.<sup>15</sup> As noted above, Jones and Bodmer present arguments both for and against according moral status to the early embryo.<sup>16</sup>

Future technical developments or altered procedures in clinical IVF research may reduce the difference of opinion between the two points of view on the moral status of the fetus. For example, an improved rate in the success of implantation following IVF and embryo transfer might counter the Hellegers-McCormick objection to excessive embryo loss, at least in part. The practice of fertilizing only one oocyte per attempted transfer, while preserving any remaining oocytes by freezing for future IVF and embryo-transfer attempts, would resolve much of the "discard" problem. However, it seems clear that genetically abnormal early embryos



will continue to be discarded in the future.

b. The naturalness or artificiality of laboratory-assisted reproduction. Several commentators have discussed a second presupposition of the IVF debate, namely, whether the acts of IVF and embryo transfer themselves violate a natural order or structure for human procreation. This issue is at least logically distinguishable from the question whether the widespread adoption of IVF as a method of reproduction would have deleterious social consequences. Three positions on the question of naturalness can be identified: (1) the view that natural reproduction is inherently superior in a moral sense; (2) the view that artificial methods can be justified when natural reproduction is impossible; and (3) the view that artificial methods of reproduction are inherently superior.

Leon Kass is perhaps the most vigorous advocate of the view that natural reproduction is inherently superior. He writes:

Is there possibly some wisdom in that mystery of nature which joins the pleasure of sex, the communication of love, and the desire for children in the very activity by which we continue the chain of human existence?

\*\*\*

My point is simply this: there are more and less human ways of bringing a child into the world. I am arguing that the laboratory production of human beings is no longer human procreation, that making babies in laboratories -- even "perfect" babies -- means a degradation of parenthood.<sup>17</sup>

In a similar vein, Pope Pius XII in 1956 opposed artificial insemination by arguing that

A child is the fruit of conjugal union when this union is fully expressed by the bringing into play of the organic functions and the sensory emotions attached to them, and of the spiritual and disinterested love which animates this union. It is

in the unity of this human act that the biological conditions of generation must be posited.<sup>18</sup>

Later in the same address, Pius XII remarked without further elaboration, "On the subject of attempts at artificial human fecundation 'in vitro', let it suffice for Us to state that such attempts must be rejected as immoral and absolutely unlawful."<sup>19</sup> Paul Ramsey, while accepting artificial insemination by the husband in carefully delimited circumstances, expresses great sympathy for the position of Kass and Pius XII on the unnatural character of IVF and embryo transfer.<sup>20</sup>

A mediating view is adopted by Rabbi Immanuel Jakobovits,<sup>21</sup> moral theologian Charles Curran,<sup>22</sup> and Hellegers and McCormick.<sup>23</sup> These commentators argue that there is no inherent objection to IVF and embryo transfer in cases where conception by the usual method is impossible. All four authors add the proviso that the question of risks to the potential offspring must be considered as an independent criterion of the rightness or wrongness of clinical IVF. While R. G. Edwards does not explicitly adopt the mediating view, he does note (contra Kass) that, compared with widely-used methods of contraception, IVF and similar reproductive techniques have contributed relatively little to the separation of sex and reproduction.<sup>24</sup> Callahan challenges Kass's sharp distinction between the "natural" and the "artificial," arguing that it is also natural for human beings to create culture and that technology is a part of that culture.<sup>25</sup>

Taking Callahan's argument one step further, Joseph Fletcher adopts a third position on "the natural." In his view, "technology cannot be 'against nature' because in that case it simply could not work."<sup>26</sup> Indeed,

according to Fletcher, what is called "nature" is often nothing more than blind chance, the antithesis of rational human control.

Should we leave the fruits of human reproduction to take shape at random, keeping our children dependent on the accidents of romance and genetic endowment, of sexual lottery on what one physician calls "the meiotic roulette of his parents' chromosomes"? Or should we be responsible about it, that is, exercise our rational and human choice, no longer submissively trusting to the blind worship of raw nature?<sup>27</sup>

## 2. Ethical Issues Related Primarily to Individual Research Subjects

Since the first modern code of research ethics was formulated at Nuremberg, numerous similar codes have been formulated, disseminated, and discussed. Recurrent themes can be identified in these codes, for example, the importance of risk-benefit analysis and informed consent in any proposed research involving human subjects.<sup>28</sup> The following section seeks to illustrate how the general themes discussed in the codes of research ethics have also been addressed in debates about the ethics of IVF and embryo transfer.

a. The need for clinical IVF research. There are at least four senses in which the need for IVF has been discussed.

How many women who wish to bear children are infertile because of tubal occlusion?

Of these infertile women, how many need IVF in the sense of having no alternative means for producing children of their own?

Is the desire to have children who are biologically one's own really a medical need?

To what extent is clinical IVF research needed, when one considers other needs for health-care services?

The fourth question will be reserved for discussion under the heading of allocation (I.A.3.b.).<sup>\*</sup> The first three questions will be addressed here.



The extent of infertility due to tubal occlusion is an empirical question, subject to further research. R. G. Edwards estimates that in the United Kingdom approximately two per cent of all women suffer from tubal occlusion.<sup>29</sup> A study sponsored by the National Research Council estimated that between one-half and one percent of all women might be helped by IVF and embryo transfer. The same study added that the current need could be reduced by a decline in rates of puerperal sepsis and gonorrhea or raised by an increase in the number of women who decide to have children after having elected voluntary sterilization by tubal ligation.<sup>30</sup>

The issue of alternative means of overcoming infertility due to tubal occlusion is again an empirical question. Here estimates vary. Leon Kass argues that surgical reconstruction of the oviduct should be the preferred alternative to IVF and embryo transfer. Kass continues, "At present, the success rate for oviduct reconstruction is only fair, but with effort and practice this is bound to improve."<sup>31</sup> Ramsey notes that thirty to fifty percent success rates in the reconstruction of damaged oviducts have been reported.<sup>32</sup> In contrast, R. G. Edwards cites an estimate that probably only one-fifth of women with damaged oviducts would be helped to achieve fertility by surgical reconstruction of their oviducts.<sup>33</sup>

The third way of stating the need-question -- Is infertility really a medical need? -- moves beyond the realm of empirical data to raise basic philosophical questions about the nature of health and disease and the proper role of the health professions. Kass argues that infertility is not a disease in the strict medical sense and that a physician who employs IVF to overcome infertility is merely treating the desire of the woman or couple to bear a child. Moreover, Kass notes, IVF and embryo transfer do not resolve the underlying infertility problem of the woman: "She remains

as infertile as before."<sup>34</sup> Paul Ramsey echoes Kass's view, arguing that IVF concentrates on a product and "is therefore manufacture by biological technology, not medicine." In a footnote Ramsey adds that if one were to counter his argument by citing medicine's substantial technological armamentarium, one would be tacitly reducing the child produced by IVF "to the status of a prosthesis for his mother's condition."<sup>35</sup>

R. G. Edwards and David Sharpe presuppose a somewhat broader concept of disease. They concede that "The physical health of parents does not demand that their infertility be cured." However, they continue, "the desire to have children must be among the most basic of human instincts, and denying it can lead to considerable psychological and social difficulties."<sup>36</sup> Without elaborating a philosophy of health care, Edwards and Sharpe assert simply that "Infertility seems to be a clinical defect to be remedied if possible by medical attention."<sup>37</sup> As for Kass's argument that the infertile woman who bears a child by means of IVF is not cured of her disease, Edwards replies that "most medical treatment, particularly of constitutional or genetic disorders, is similarly symptomatic in nature."<sup>38</sup> Edwards cites insulin, false teeth, and spectacles as three examples of medical treatments which do not correct the patient's clinical condition but merely modify its expression.

b. The need for and adequacy of prior laboratory research, including animal research, on IVF and embryo transfer. One of the standard prerequisites for ethically-acceptable research designs in human research is the conduct of appropriate prior laboratory studies. In the words of the revised Declaration of Helsinki (1975), "Biomedical research involving human subjects...should be based on adequately performed laboratory and

and animal experimentation...."<sup>39</sup> Judgments about the adequacy or inadequacy of prior laboratory research include both empirical and evaluative components.

In published discussions of clinical IVF two views on the adequacy of prior laboratory studies can be identified. Several commentators -- among them Kass,<sup>40</sup> Marc Lappe,<sup>41</sup> Benjamin Brackett,<sup>42</sup> and Luigi Mastroianni<sup>43</sup> -- argued between 1971 and 1973 that further animal research was required before clinical application of IVF and embryo transfer to humans was attempted. During Congressional hearings on IVF held in August 1978 Brackett reiterated his view that additional animal research should precede clinical research with human beings.<sup>44</sup>

Several arguments are advanced by proponents of additional animal research. First, the number of species and the total number of animals born following IVF and embryo transfer are both quite low. In the words of Brackett, "Less than 200 rabbits, a similar number of mice and less than 50 rats have been born following conception in vitro. Most of these offspring are accounted for in 14 published reports on the rabbit, seven on the mouse and one on the rat."<sup>45</sup> Second, few studies involving primates<sup>46</sup> or non-litter-bearing mammals like the cow<sup>47</sup> have been performed. Third, animal research performed to date has devoted insufficient attention to the question of possible abnormalities in products of IVF.<sup>48</sup>

In contrast, R. G. Edwards and Landrum Shettles<sup>49</sup> argue that the quantity and quality of animal research on IVF are sufficient to justify clinical IVF research efforts. The primary arguments for proceeding to human studies are summarized by Edwards as follows: (1) data have been published on several animal species which indicate that preimplantation embryos are highly resistant to malformation due to IVF or embryo transfer;



(2) for other areas of scientific research -- e.g., studies of kidney transplantation, vasectomy, oral contraception, and teratogenesis -- studies in primates have not been required; research in several sub-primate species of mammals has been considered sufficient; and (3) many infertile couples would lose the opportunity to bear children of their own if the clinical application of IVF were delayed until the completion of studies in non-human primates.<sup>50</sup>

It is perhaps worthy of note that the initial draft of proposed DHEW guidelines for IVF research, published in November 1973, contained the following stipulation:

No research involving the implantation of human ova fertilized in the laboratory should be supported until the appropriate scientific review boards are satisfied that there has been sufficient work in animals (including sub-human primates) to demonstrate the safety of the technique. It is recommended that this determination of safety include studies of natural born offspring of the products of in vitro fertilization.<sup>51</sup>

The preamble to the initial revision of these proposed rules, published in August 1974, required only that "animal studies" be performed:

With respect to implantation of fertilized human ova, it is expected that the [Ethical Advisory] Board will consider such factors as the safety of the technique (with respect to offspring) as demonstrated in animal studies, and clarification of the legal responsibilities of the donor and recipient parent(s) as well as the research personnel.<sup>52</sup>

c. Risks of clinical IVF research to the potential product of IVF. As noted above, more discussion seems to have been devoted to this issue than to any other single question in the IVF debate. This review can provide only a brief summary of the major arguments.

If one examines the basic structure of the risk-argument in discussions

of IVF, one can identify four distinct syllogisms. Three of the syllogisms share the same major premise; two reach the same conclusion. For this comparison of syllogisms, it will be useful to reverse the order followed in previous sections of this review; that is, the argument of proponents of clinical IVF research will here be followed by the arguments of opponents.<sup>53</sup>

The first two syllogisms proceed from the issue discussed in the previous section, the adequacy of prior laboratory research. The position of Edwards,<sup>54</sup> Shettles,<sup>55</sup> and Jones and Bodmer<sup>56</sup> is epitomized in the first syllogism:

- A<sub>1</sub>. No clinical research should be performed until prior laboratory research has provided an adequate basis for estimating the likely risks to human subjects.
- B<sub>1</sub>. In the case of clinical IVF and embryo transfer sufficient prior laboratory research has been done.
- C<sub>1</sub>. Therefore, clinical research on IVF and embryo transfer may proceed.

Kass,<sup>57</sup> Mastroianni,<sup>58</sup> Brackett,<sup>59</sup> Lappé,<sup>60</sup> the National Research Council study,<sup>61</sup> and Jakobovits<sup>62</sup> accept the same major premise but directly contradict the minor premise and therefore reach the opposite conclusion:

- A<sub>1</sub>. No clinical research should be performed until prior laboratory research has provided an adequate basis for estimating the likely risks to human subjects.
- B<sub>2</sub>. In the case of clinical IVF and embryo transfer insufficient prior laboratory research has been done.
- C<sub>2</sub>. Therefore, no clinical research on IVF and embryo transfer should be performed at this time.

Since the minor premise of this syllogism is based on an assessment of the current state of the art in laboratory research, it is possible that additional laboratory results could lead proponents of this syllogism to adopt the opposite minor premise and thus reach the opposite conclusion.

In some passages several commentators -- particularly Kass,<sup>63</sup> Ramsey,<sup>64</sup> and the National Research Council study<sup>65</sup> -- seem to espouse a third syllogism. Again the major premise is the same.

- A<sub>1</sub>. No clinical research should be performed until prior laboratory research has provided an adequate basis for estimating the likely risks to human subjects.
- B<sub>3</sub>. Prior laboratory research can never provide a basis for estimating the likelihood of some very important potential risks to the products of IVF, e.g., the risk that early manipulation in vitro will cause mental retardation in some products of IVF.
- C<sub>3</sub>. Therefore no clinical research on IVF and embryo transfer should ever be performed.

Persons who adopt this syllogism have concluded that the risks of clinical IVF research are not only unknown but unknowable. Additional laboratory research would therefore seem to be irrelevant and the minor premise and conclusion of the syllogism irreversible.

A further syllogism is advanced particularly by Paul Ramsey<sup>66</sup> and echoed by Leon Kass<sup>67</sup>. This syllogism begins at a different point from the preceding three but reaches the same conclusion as the third:

- D<sub>1</sub>. No clinical research should be performed if it employs immoral means to achieve its goal, e.g., the goal of alleviating infertility.
- E<sub>1</sub>. The anticipated production of at least some deformed or retarded infants and children during the early stages of clinical IVF research is an inherently immoral means.
- C<sub>3</sub>. Therefore, no clinical research on IVF and embryo transfer should ever be performed.

This fourth syllogism raises the issue of acceptable levels of risk in clinical IVF research. Kass and Ramsey seem to argue that the "Do no harm" principle requires that the risk of harm be positively excluded.



Fletcher, however, argues that a guarantee of benefit or absence of harm in clinical research is impossible and that no-harm stipulations could bring all human research to a halt.<sup>68</sup> Fletcher,<sup>69</sup> Lappé,<sup>70</sup> and Curran<sup>71</sup> would find the risks of clinical IVF research acceptable if those risks were equivalent to or less than the risks of in vivo reproduction.

In the literature on clinical IVF the discussion of risks sometimes oscillates between two types of risks -- risks to embryos or fetuses and risks of an untoward event, namely, the birth of an abnormal infant. Risk-reduction in the latter sense might include the selecting out of defective early embryos and the abortion of fetuses in which genetic defects, chromosomal aberrations, or developmental abnormalities are detected by various methods of prenatal diagnosis. James Watson has even suggested, perhaps in an effort to stimulate discussion, that the physician attending the birth of a product of clinical IVF should have "the right to terminate [the] baby's life should it come out grossly abnormal."<sup>72</sup> Edwards advocates the use of prenatal risk-reduction measures.<sup>73</sup> To Ramsey, however, such measures seem rather to increase the risk to the embryo or fetus.<sup>74</sup>

There is one philosophical problem which lurks in the background of discussion concerning risks to products of IVF. In this general review the problem can only be identified, not analyzed in detail. When one speaks of risks to the products of IVF, one is frequently referring to risks to potential rather than actual entities. These potential entities can be divided into two classes. "The unconceived<sub>1</sub>", which have not been conceived and which will never be conceived, are entirely free from risks. "The unconceived<sub>2</sub>", which have not yet been conceived but which will be conceived in the future, will from the time of their conception be subject to a variety

of risks, some of which will be the result of pre-conception events. If one assumes that a particular couple can conceive a child that is biologically their own by means of IVF and embryo transfer, then one is faced with the difficult task of comparing the situation of "an unconceived entity" in the first sense with that of an entity which, thanks to IVF, may only be "unconceived" in the second sense. It is around the same conundrum that at least a part of the wrongful life debate revolves.<sup>75</sup>

d. Risks of clinical IVF research to the oocyte donor.<sup>76</sup> In the literature on the ethics of IVF and embryo transfer relatively little attention has been devoted to risks to the would-be mother. Specific risks which have been identified are: (1) pretreatment of the woman with hormones to induce superovulation, a therapy which occasionally produces ovarian cysts;<sup>77</sup> (2) removal of oocytes by means of laparoscopy, a surgical procedure which requires general anesthesia;<sup>78</sup> (3) potential damage to the uterus during embryo transfer;<sup>79</sup> and (4) the risks which accompany careful monitoring of the pregnancy, for example, the risks of amniocentesis.<sup>80</sup> To these risks may now be added a fifth, which was reported subsequent to the publication of most ethical analyses -- namely, the risk of ectopic pregnancy.<sup>81</sup> The National Research Council study describes various of these risks as "known small risks" and "probably small but unknown risks."<sup>82</sup> R. G. Edwards<sup>83</sup> and Luigi Mastroianni<sup>84</sup> regard the first four risks as minimal and as comparable to the risks of standard therapy for infertility and of sterilization by tubal ligation.

e. Informed consent by participants in clinical IVF research. There is unanimous agreement among commentators on the ethics of clinical IVF research that the informed consent of the would-be mother (and presumably

of both parents) must be secured prior to the initiation of the research.<sup>85</sup> In addition, some commentators have argued that the consent issue is relevant to the potential product of clinical IVF, as well. These two distinct aspects of the consent question will be discussed in turn.

In the consent transaction with the would-be parents, several specific items of information have been identified by various commentators as material to the decision of the couple: (1) the availability of potentially efficacious alternative therapies, e.g., surgical reconstruction of the oviducts;<sup>86</sup> (2) the anticipated need for repeated laparoscopies; (3) the low probability of success; (4) the likelihood that the primary beneficiaries of the research will be other couples rather than the research participants themselves;<sup>87</sup> (5) the source of the gametes to be used in the attempted IVF (i.e., a guarantee that only the sperm and oocytes of the couple will be employed);<sup>88</sup> and (6) the disposition to be made of sperm, oocytes, and embryos not required for the transfer attempt.<sup>89</sup>

Several commentators have remarked that infertility patients may have a diminished capacity for voluntary consent because of their desperate desire for children.<sup>90</sup> The report of the National Research Council also suggests that physician-researchers may experience conflicts in their dual roles, hoping on the one hand to alleviate the infertility of a particular couple but desiring on the other hand to carry out laboratory research with surplus oocytes, sperm, and embryos. Without explicitly endorsing such measures, the report notes the potential value of special standards or procedures and special licensure for clinicians who also function as researchers.<sup>91</sup>

R. G. Edwards acknowledges the importance of the consent issue. However,



he argues that there are grounds for being confident that the problems of consent are not insuperable.<sup>91</sup>

Many infertile couples urgently desire the work on fertilization and implantation to proceed, wish to help with it, and are fully capable of understanding their condition and the attempts to cure it. A significant proportion are doctors or the wives of doctors, scientists, solicitors, clerics, and other members of the community who are articulate, discriminating, and fully capable of analyzing and judging social and medical situations....They are evidently aware, too, that the methods might not work, their fertility remain uncured, and that other women may be the ultimate beneficiaries of the developing methods.<sup>92</sup>

A second dimension of the consent issue is presented by Leon Kass and Paul Ramsey, who regard clinical IVF research as unethical research on the unconceived and the unborn. At some points in the Kass-Ramsey analysis a concern about imposing substantial risk on a research subject which cannot consent seems paramount, as when Kass argues:

It is one thing voluntarily to accept the risk of a dangerous procedure for yourself (or to consent on behalf of your child) if the purpose is therapeutic ....It is quite a different thing to submit a child to hazardous procedures which can in no way be therapeutic for him....This argument against non-therapeutic experimentation on children applies with even greater force against experimentation "on" a hypothetical child (whose conception is as yet only intellectual). One cannot ethically choose for him the unknown hazards he must face and simultaneously choose to give him life in which to face them.<sup>93</sup>

At other points Ramsey argues that "unless every possibility of damage from the procedure itself has surely been foreclosed," one should not "manipulate a patient into being."<sup>94</sup> What Ramsey seems specifically to object to is the notion of deliberately bringing a being into existence when one knows in advance that the being will inevitably be the subject of research and when the subject will clearly not be able to consent to participation

in the research. On this view, the level of potential research risk is less important than the fact of unconsented involvement in research.<sup>95</sup>

Joseph Fletcher and R. G. Edwards deny the relevance of consent by the unconceived or the unborn. Both authors comment that embryos, fetuses, and infants conceived by the conventional method do not, and indeed cannot, consent in advance to their conception.<sup>96</sup> In Edwards' view, Ramsey's position would lead to a "total negation" of prenatal medicine: one would not recommend a sleeping pill, amniocentesis, or a Caesarean section to a woman for fear of disturbing the fetus.<sup>97</sup>

f. Liability or compensation for IVF-research-related injury. Discussion of liability frequently considers the question whether a successful action for damages could be brought in a court of law. The focus of this section, however, is on the moral responsibilities of clinical investigators or parents in the event of injury to the woman or the child produced by clinical IVF research.

There is little explicit discussion of moral responsibility for injuries in the ethical literature on clinical IVF. The entire debate concerning the acceptability of the risks of clinical IVF research (see I.A.2.c. and d.) is of course germane to the moral-responsibility issue. Those who argue that the risks are currently or for all time unacceptable would no doubt hold the parents and/or investigators responsible for any injuries which do occur. Conversely, proponents of proceeding with the research would probably respond to an injury by asserting that the research risks had been minimized and that the damages had resulted from causes beyond human control.

Various analogies have been proposed to illuminate the moral-responsibility question, particularly with respect to the product of clinical IVF.

Jakobovits compares proposals to proceed with clinical IVF research with the "indecent haste" which in his view characterized the early stages of heart-transplant surgery.<sup>98</sup> The analogy is imperfect, however, in the sense that heart transplantation aims to prolong the life of an already existing person, usually an adult. Other commentators have suggested parallel cases in which either a novel or a somewhat risky procedure is employed during pregnancy for the sake of fetal health -- for example, the use of steroids in an effort to avoid spontaneous abortion<sup>99</sup> or the use of Caesarean section as a method of delivery.<sup>100</sup> These analogies are somewhat closer to the question of clinical IVF research since they involve the prenatal stages of life and may influence whether a fetus attains viability or live birth. However, the closest parallels to the situation of the hypothetical product of IVF are those which involve the effort to begin a pregnancy in circumstances which deviate in some respect from "the normal." The following situations are perhaps illustrative:

The wife in an infertile marriage takes hormone treatments in an effort to become pregnant.<sup>101</sup>

An infertile couple requests the use of artificial insemination with the husband's sperm in the hope of having a child.<sup>102</sup>

A couple in which the wife is over 40 decides to conceive an additional child, knowing that the risk of chromosome abnormalities increases with advancing natural age.

A couple in which both members carry a recessive genetic trait for a serious disease decides nonetheless to conceive a child.<sup>103</sup>

A couple living in abject poverty with inadequate food and housing decides to have a child.<sup>104</sup>

In all of these cases there is, or at least may be, a higher than average risk to the hypothetical child, yet that risk accompanies the transition from



nonexistence to existence for the child-to-be.

It is this transition from nonexistence to existence which also complicates the moral question of possible compensation for injury. In a report of the DHEW Secretary's Task Force on the Compensation of Injured Research Subjects, the following definition of injury is proposed:

[Injury is] harm, disability or death suffered by a subject of biomedical and behavioral research...where such injury is (1) proximately caused by such research, and (2) on balance exceeds that reasonably associated with such illness from which the subject may be suffering, as well as with treatment usually associated with such illness at the time the subject began participation in the research.<sup>105</sup>

In the case of clinical IVF research, the issue of proximate causation would be highly complex in itself.<sup>106</sup> However, the second clause in this careful definition would be even more difficult to apply since it assumes an injury to an already-existing person. Could one adapt the definition to cover the case of a child conceived by means of IVF? If so, how would one compare existence in a damaged condition with nonexistence?<sup>107</sup> If not, would one want to exclude all products of in vitro fertilization from the class of subjects eligible for compensation -- at least for injuries apparently caused by the IVF and embryo transfer procedure?<sup>108</sup>

### 3. Broader Social and Public Policy Issues

a. Potential long-term consequences of clinical IVF research. Proponents and opponents of current clinical IVF research efforts alike have identified several potential consequences of the research:

1. The donation of ova or embryos to third parties.<sup>109</sup>
2. The gestation of embryos and fetuses in surrogate mothers.<sup>110</sup>
3. The establishment of human ovum and embryo banks.<sup>111</sup>
4. Sex determination of embryos prior to implantation.<sup>112</sup>
5. The screening of embryos for genetic or chromosomal defects prior to implantation.<sup>113</sup>

6. The production of chimeric embryos through the injection of cells from one blastocyst into another.<sup>114</sup>
7. The repair of genetic defects prior to implantation.<sup>115</sup>
8. Replacement of the haploid nucleus of an oocyte with the diploid nucleus of a donor cell, i.e., cloning.<sup>116</sup>
9. Modification of the early embryonic genotype in order to introduce desired characteristics, i.e., genetic engineering.<sup>117</sup>
10. Extracorporeal gestation, or ectogenesis.<sup>118</sup>

Several of these potential consequences will be analyzed in greater detail in later sections of this paper. Here it will be sufficient to note two general types of disagreements concerning the techniques and practices enumerated above.

There is, first, debate concerning the likelihood that some of the techniques will ever be (1) feasible or (2) practical on a wide scale even in the absence of legal restrictions. Biologist James Watson, for example, expresses concern that "a human being -- born of clonal reproduction -- most likely will appear on the earth within 20 to 50 years."<sup>119</sup> In contrast, theologian G. R. Dunstan chides his colleague, Paul Ramsey, for failing to adequately distinguish between "notional possibilities in biochemical theory" and "what is actually foreseeable in practice."<sup>120</sup>

Evaluations of the potential long-term consequences of clinical IVF research also differ. Three distinct positions can be identified. Leon Kass and Paul Ramsey oppose clinical IVF research in part because they view it as "a giant step toward the full laboratory control of human reproduction."<sup>121</sup> For Joseph Fletcher and Bentley Glass, on the other hand, the potential consequences of clinical IVF research constitute a welcome liberation from coital-gestational reproduction and a means to reduce the incidence of genetic defects.<sup>122</sup> R. G. Edwards takes a mediating position, arguing for the potential clinical value of some

techniques, e.g., sex determination, while expressing reservations about the donation of embryos and cloning.<sup>123</sup>

b. Appropriate allocation of research and clinical resources to clinical IVF research and to other areas of research or health care. Few commentators have discussed the allocation issue, perhaps because they regard allocation discussions as being primarily matters to be determined by the public budgetary process, peer review of research proposals, and the priorities of private foundations.

The National Research Council study includes a brief reference to the allocation problem:

Questions concerning the financial costs of the procedure (physicians' fees, special facilities, training of special agents) or the burdens it may place on the health-care system (by diverting funds and personnel needed to meet more compelling needs) may be raised, especially if the technology should come into widespread use.<sup>124</sup>

André Hellegers and Richard McCormick restate the same objection in other words:

With limited resources should our country be pouring money into life-creating technologies when basic health needs go unmet?....We are not arguing against medical progress, for a great deal of useful knowledge is potentially available through in vitro research. We are simply concerned that Americans spell out carefully what progress means before they endorse it.<sup>125</sup>

Hellegers and McCormick go on to argue that the establishment of embryo transfer centers would require a major financial investment and that the services of such centers would probably be inaccessible to the poor, who, the authors note, suffer from a higher incidence of tubal obstructions than do the more well-to-do.<sup>126</sup>

Proponents of clinical IVF research have discussed the allocation



question even less than critics of the research. R. G. Edwards does comment that "The cost [of embryo transfer] is very small, if it should be thought an important point to judge the economics of the treatment."<sup>127</sup> If confronted with the allocation question, advocates of the research would probably also reiterate the need-argument noted earlier -- namely, that thousands of women suffering from obstruction of the oviducts cannot be helped by conventional techniques and would, without the aid of the procedures being developed in clinical IVF research, be condemned to permanent sterility.

c. Appropriate institutional frameworks for the provision of advice on or monitoring of clinical IVF research. Commentators on the ethics of clinical IVF research have focused primary attention on three possible institutional responses to the research: (1) the establishment of international standards for the conduct of the research; (2) the creation of advisory committees which could be consulted voluntarily by researchers in the field; and (3) the imposition by the research community itself of a temporary moratorium on clinical IVF research.

James Watson, perhaps because he had been asked to testify on international science policy before a House panel, initiated the discussion of developing international standards. In his view, unilateral action by the United States would be ineffectual, particularly since British research in experimental embryology was in 1971 considerably further advanced than similar research in the United States.<sup>128</sup> Leon Kass<sup>129</sup> and Marc Lappe<sup>130</sup> later reiterated Watson's call for international research guidelines.

The advisory-committee mechanism was proposed by Edwards and Sharpe, as well as in a Nature editorial, in May 1971. In the words of Edwards and Sharpe,

If some form of regulation is required, what is needed is not heavy handed public statute, or rule-making committees, or the conscience of individual doctors, but a simple organization easily approached and consulted to advise and assist biologists to reach their own decisions ....In line with the stress on individual scientific responsibility, advisers are needed whose achievement and attitudes make them worth listening to in matters affecting the future of human research -- doctors, scientists, lawyers, authors, and other laymen -- because they are broadly talented people, not because they serve ex officio as formal representatives of their professions, societies, or constituencies.<sup>131</sup>

Nature's editorial response to the Edwards-Sharpe proposal observed that their suggested forum might be too broad and that "a good beginning could be made within the framework of academic science and medicine."<sup>132</sup>

At the same time, on the other side of the Atlantic, then-Senator Mondale proposed the creation by Congress of a National Advisory Committee on Health Science and Society.<sup>133</sup> James Watson, in an interview published in May 1973, expressed support for Mondale's advisory commission concept as an appropriate mechanism for informing the Congress about scientific developments like IVF and cloning.<sup>134</sup> Joseph Fletcher expressed sympathy for Mondale's proposal but also warned that "The no-no forces will want to use the Commission to crack down with police powers..."<sup>135</sup>

A third suggested response to possible developments in clinical IVF research was a call for a temporary self-imposed moratorium. Immanuel Jakobovits issued such a call in Great Britain in March 1970.<sup>136</sup> In the United States Leon Kass proposed a profession-wide self-imposed moratorium "at least until the safety of the procedures can be assessed and assured."<sup>137</sup> Marc Lappe and the American Medical Association<sup>139</sup> seconded Kass's suggestion in 1972.

An approach which incorporates elements from the second and third

proposals outlined above has in fact been followed in the United States since late 1973 -- at least for research funded by DHEW. Beginning in November 1973, the proposed rules and regulations of the Department have required that all departmentally-supported research involving human IVF be reviewed by an Ethical (now Ethics) Advisory Board. In the successive drafts of the DHEW rules (November 16, 1973;<sup>140</sup> August 23, 1974;<sup>141</sup> and August 8, 1975<sup>142</sup>), the criteria for the Board's review of IVF research proposals have gradually been reduced from an explicit set of rules, to suggested issues for consideration, to the simple requirement that the Board render its advice concerning each application's "acceptability from an ethical standpoint."<sup>143</sup> The effect of this review requirement, at least since the formal promulgation of regulations in August 1975, has been to impose a moratorium on any DHEW-funded human IVF research, whether clinical or basic.

#### 4. Special Case: Potential Psychosocial Complications Resulting from the Donation and Receipt of Sperm, Oocytes, or Embryos

Until now this review has considered ethical issues raised by clinical IVF in the simplest paradigm case, the case which involves only the members of an established heterosexual couple in the provision of gametes and the subsequent gestation of the product of IVF. Numerous other scenarios have been developed which involve third parties in the donation or transfer of sperm, oocytes, or embryos. Among these scenarios the two which have received the most discussion are (1) the use of donated oocytes in IVF and (2) the transfer of the early embryo to the uterus of a third party, the surrogate or host mother, for gestation and delivery.

There is consensus among virtually all commentators that both of these alternative paradigms raise more complex ethical (and legal) questions than



the simple couple-centered paradigm discussed heretofore. The commentators also agree that the second case -- gestation in a host mother -- is more problematic than the first.

The most-discussed example of the first paradigm involves the combination of donated oocytes with the husband's sperm in the IVF-procedure and the subsequent transfer of the early embryo to the uterus of the wife.<sup>144</sup> This combination is closely analogous to artificial insemination using sperm from a donor (AID). Suggested reasons for a couple's resorting to the use of donated oocytes are the inability of the would-be mother to produce fertilizable ova or her knowledge that she carries a dominant or X-linked recessive genetic defect.<sup>145</sup>

Evaluations of the use of donated oocytes in clinical IVF research generally parallel conflicting assessments of AID. Some critics -- among them Immanuel Jakobovits,<sup>146</sup> Bernard Häring,<sup>147</sup> and Paul Ramsey<sup>148</sup> -- object to the introduction of third-party gametes into the relationship of an established couple, in part because of the potential psychological effects on the infertile partner and in part because of problems surrounding disclosure or nondisclosure to children of the circumstances of their conception. In addition, the National Research Council study argues that the inconvenience of oocyte donation and the consequent scarcity of oocytes may lead to debates about appropriate financial compensation of donors as well as to the establishment of commercial oocyte banks.<sup>149</sup> On the other hand, Joseph Fletcher asserts that

Egg grafts or artificial enovulations from a donor would be perfectly ethical if a person is, for example, without ovaries or has a hopeless infection of her tubes, or if she fears to pass on a genetic disease. A transfer is psychologically happier than AID because the husband is the genetic father and the woman can at least "carry" her own baby if she wants.<sup>150</sup>

R. G. Edwards adds that, in his view, "oocyte transfer should be as acceptable [as AID] ethically and legally...in the rare cases where it is needed."<sup>151</sup>

A second type of case would hypothetically involve the transfer of an early embryo to the uterus of a surrogate mother for gestation and delivery. Medical contraindications or obstacles to the oocyte donor's becoming pregnant might include cardiac disorders, partial paralysis, repeated miscarriages, or hysterectomy. Social reasons for the oocyte donor's reluctance to carry a fetus to term might be career plans or the desire to avoid the discomforts of pregnancy.<sup>152</sup>

Commentators on the ethics of IVF have raised several objections to surrogate-motherhood proposals:

1. Custody conflicts concerning the child could arise between the genetic parents on the one hand and the surrogate mother on the other.<sup>153</sup>
2. The surrogate mother might, contrary to the wishes of the genetic parents, adopt a lifestyle which was likely to damage the embryo or fetus.<sup>154</sup>
3. The genetic parents might require the surrogate mother to undergo amniocentesis and, in the event a genetic or chromosomal abnormality were detected in the fetus, to undergo a mid-trimester abortion.<sup>155</sup>
4. The child might be born with serious physical and/or mental handicaps, and the genetic parents might therefore refuse to accept it.<sup>156</sup>
5. Poor women, lacking similarly-lucrative alternative job possibilities, might be coerced into accepting surrogate motherhood by a combination of familial financial pressures and the monetary inducement offered by the well-to-do.<sup>157</sup>

For one or more of these reasons, proposals to employ IVF for surrogate motherhood are rejected by most commentators on the ethics of IVF -- including R. G. Edwards,<sup>158</sup> James Watson,<sup>159</sup> a British Medical Association panel,<sup>160</sup> Immanuel Jakobovits,<sup>161</sup> Bernard Häring,<sup>162</sup> Paul Ramsey,<sup>163</sup> and

Leon Kass.<sup>164</sup>

While conceding the possibility of psychological or legal complications in surrogate motherhood, Joseph Fletcher queries: "If a wetnurse can supply another woman's child with her milk, and if we can give our blood to others, than how could there be any moral barriers to donating even some basic gifts, such as...placental sustenance, in hostess gestation?"<sup>165</sup> In a similar vein, Laurence Karp and Roger Donahue report having received office calls from a few women who inquired

whether they might volunteer their services should [surrogate motherhood] ventures become a reality. They state that they love being pregnant, and would arrange to always be in this condition if it were not for the matter of having to keep the babies. They think that hiring out their uteri would be a fine way to make a living.

The authors conclude:

On reflection, it seems inconsistent to categorically deny such women this kind of livelihood while we permit and even encourage people to earn money by such dangerous means as coal mining, or racing little cars around a track at 200 miles per hour.<sup>166</sup>

The views of two lawyers concerning the legalization, as distinguished from the ethical evaluation, of surrogate motherhood may be noted in passing. Mariel Revillard, a French attorney, advocates state sanction of surrogate motherhood in cases where pregnancy in the oocyte donor is medically contraindicated, but not for "any other motivation -- coquetry, ambition or pursuit of a career where aesthetics are essential."<sup>167</sup> Philip Reilly argues that the state should not interfere with the right of individuals to contract for surrogate-motherhood services. Instead, Reilly suggests, the state should adopt procedural safeguards, a "Uniform Embryo Transfer Act," to clarify the responsibilities of the contracting parties and to forestall



the development of problems like those identified by critics of surrogate-motherhood proposals.<sup>168</sup>

#### B. Basic Research

The present section focuses on basic laboratory research involving early human embryos. In this type of research no effort is made to transfer embryos to the uterine environment for gestation and delivery. Instead, the research effort is directed toward the development of a knowledge base which, it is hoped, will one day contribute to the achievement of such goals as the promotion of fertility, the provision of more adequate contraceptive measures, and the prevention or repair of genetic and chromosomal abnormalities.

Scientists familiar with research on non-human mammalian embryos have suggested several areas of research which, from a technical standpoint, could be explored in the near future with the aid of laboratory research on human embryos. Among these areas are the following:

1. Mechanisms of fertilization
2. Chromosomal behavior
3. Cellular growth and differentiation
4. The control of gene activity
5. Biochemical pathways
6. The effects of environmental factors, e.g., radiation, freezing, and various chemicals, on fertilization and early development.<sup>169</sup>

Techniques employed in the study of these topics would include fertilization in vitro, in vitro culture of early embryos through any stage of development up to and including the blastocyst stage,<sup>170</sup> the fusion of embryonic cells with other cells, the infection of embryonic cells with viruses, the introduction of various changes (chemical or temperature changes, for example) into the embryonic environment, the recombination of DNA from embryonic cells with DNA from other organisms, biochemical assays of embryonic cells, and microscopic analysis of embryonic cells.<sup>171</sup> In short,

many if not all of the techniques employed in tissue culture and recombinant DNA research could, technically speaking, be applied to early human embryos or embryonic cells.

The literature on ethical issues in basic research on early human embryos is quite sparse, as it is for most areas of basic research. The two issues which have received the most substantial discussion are the moral status of the early embryo in the laboratory research context and the need for obtaining informed consent from oocyte and semen donors prior to combining their gametes to produce embryos for research purposes. The questions of freedom of scientific inquiry and appropriate institutional frameworks for the review and monitoring of basic research with human embryos have also been briefly addressed in the literature. Three additional issues seem to this reviewer to be implicit in published ethical discussions: the need for basic research with human embryos; the potential long-term consequences of the research; and priorities in the allocation of resources to this area of research and to other areas of research and health care. These six topics will be discussed in the following order:

1. Presuppositions: the moral status of the early human embryo in laboratory research
2. Microethical issues
  - a. The need for basic research with early human embryos
  - b. Informed consent by donors of sperm and oocytes
3. Macroethical issues
  - a. Potential long-term consequences of basic research with early human embryos
  - b. Appropriate allocation of resources to basic research with early human embryos and to other areas of research or health care
  - c. Freedom of inquiry and the development of appropriate institutional frameworks for the monitoring of basic research with early human embryos.

# 1. Presuppositions: the Moral Status of the Early Human Embryo in Laboratory Research

Commentators on the ethics of laboratory research with early human embryos have usually taken as their starting point the ethics of clinical IVF research. From this point of departure they have then moved in opposite directions. One group, perhaps represented by Karl Rahner, argues that laboratory research with human embryos raises less serious questions than clinical IVF research since it avoids the potential problems of third-party gametes in human reproduction and of potential damage to the product of clinical IVF. The other group, perhaps represented by Leon Kass, regards as immoral the initiation of human embryonic development when one knows in advance that the life of the embryo will not be sustained.

Rahner's apparent willingness to approve laboratory research with early human embryos -- or, more accurately, his unwillingness to disapprove such research -- is based in part on a factual premise. Citing the statistic alluded to above that perhaps fifty percent of all fertilized ova never implant, Rahner continues, "Will we be able to accept that 50 per cent of all 'human beings' -- real human beings with 'immortal' souls and an eternal destiny -- will never get beyond this first stage of human existence?"<sup>172</sup> This positive doubt leads Rahner to question whether laboratory research with early embryos is morally problematic.

Of course it does not follow from the fact of such an uncertainty that experiments with fertilised embryonic material are equivalent to morally indifferent experiments with mere 'things.' But it would be conceivable that, given a serious positive doubt about the human quality of the experimental material, the reasons in favour of experimenting might carry more weight, considered rationally, than the uncertain rights of a human being whose very existence is in doubt. This is <sup>173</sup> not adduced to decide the issue one way or the other....



G. R. Dunstan expresses sympathy for this point of view in his own discussion of in vitro fertilization.<sup>174</sup>

In contrast, Leon Kass raises ethical questions about the discarding of unneeded embryos in clinical IVF research.

...The situation here, though familiar, is not identical to that of abortion. For one thing, we don't start with a foetus already in utero which one reluctantly destroys, hopefully only for good reasons. Here, nascent lives are being deliberately created despite certain knowledge that many of them will be destroyed or discarded. (Several eggs are taken for fertilization from each woman, the extra ones being available for experimentation.) The foetuses killed in abortion are unwanted, usually the result of so-called accidental conception. The embryos discarded here are wanted, at least for a while; they are deliberately created, used for a time, and then deliberately destroyed. Moreover, unlike abortion, the continued life of the laboratory embryo is in conflict with no one; no claim or right of its "mother" can be invoked to justify overriding its claim or right to life. Even if there is no intrinsic wrong done by discarding at the blastocyst stage -- and I am undecided on this question -- there certainly would be at later stages.<sup>175</sup>

One suspects that if Kass questions the moral legitimacy of discarding embryos not selected for embryo transfer, he would be unlikely to approve the creation of embryos for research purposes alone. Bernard Haring leaves no doubt about his negative verdict on laboratory research with early human embryos. Expressly dissenting from the opinion of Karl Rahner, Haring writes: "...The very probability that we may be faced with a human person in the full sense constitutes, in my opinion, an absolute veto against this type of experimentation."<sup>176</sup>

The 1974 version of proposed rule-making referred indirectly to the moral status of the early human embryo in the following sentence: "With respect to the fertilization of human ova in vitro, it is expected that the [Ethical Advisory] Board will consider...the ethical and legal issues surrounding the initiation of the products of such research."<sup>177</sup> This suggestion

was omitted from the final DHEW regulation on research involving fetuses, pregnant women, and in vitro fertilization, which were issued in August 1975.

## 2. Microethical Issues

a. The need for basic research with early human embryos. There are at least two senses in which the need-question might be addressed.

What types of basic research with early human embryos have been proposed, with what rationale, and with what likely consequences?

What types of knowledge can be developed only by means of research with human embryos and not, for example, by means of research with mammalian embryos of other species?

The need-question in the first sense was addressed briefly in the introduction to this section and will be considered further below under the heading "Potential long-term consequences" (I.B.3.a.). The need-question in the second sense will be discussed here.

In the literature on the ethics of IVF, relatively little attention has been paid to the question of alternatives to, or the compelling need for, basic research involving early human embryos. One of the few commentators who has explicitly addressed this issue is Luigi Mastroianni, who writes

Although animal models are useful in establishing basic knowledge, one cannot confidently make inferences from the laboratory animal to Homo sapiens. There are substantial differences in fertilization even among closely related laboratory species.<sup>178</sup>

This reviewer is not aware of any written comments by researchers which would contradict or qualify Mastroianni's thesis. However, it should be noted that there is debate among experimental embryologists concerning the current need for laboratory research involving human embryos. Further published discussion will, one hopes, serve to clarify this question.

The issue of possible alternatives to human research is raised in part because this issue played a prominent role in the deliberations of the National Commission concerning fetal research. Several of the Commission's final recommendations on research involving human fetuses contain the stipulation that fetal research should be conducted or supported by the Secretary, DHEW, only if "the purpose of such research is the development of important biomedical knowledge that cannot be obtained by alternative means."<sup>179</sup>

b. Informed consent by donor of sperm and oocytes. So far as this reviewer has been able to determine, only three documents address the issue of consent to the use of gametes for IVF and subsequent laboratory studies of resulting embryos. In an early essay on ethical issues in IVF research, R. G. Edwards notes:

When we first considered asking patients to help us, the early stages of fertilization had been accomplished in the laboratory by ourselves and our colleague, B. D. Bavister, using eggs taken from ovaries excised for clinical reasons unconnected with our studies. The clinical application of our work demanded that eggs be removed just before ovulation directly from the patients. They had to be given hormones -- four injections over 8-10 days -- followed by a minor operation (known as laparoscopy) in order to remove the eggs. The husband had to provide an ejaculate.<sup>180</sup>

Edwards goes on to detail how he and his colleagues secured informed consent from sperm and oocyte donor during the clinical phase of their studies. It is unclear from Edwards' statement -- and this review does not prejudge the issue -- whether consent standards in effect in Great Britain at the time of Edwards' earlier studies (using eggs from surgically excised ovarian tissue) would have required him and his colleagues to secure consent from the women from whom the ovarian tissue had been removed.

Leon Kass argues that in every case the use of a woman's oocytes in laboratory research should be preceded by providing her with the opportunity to give or refuse her consent.

Let me also raise some questions concerning experimentation done with eggs obtained from women undergoing ovarian surgery for clinical reasons. Do and should these women know what is going to be done with their eggs? To whom belong the rights governing ordinary tissue removed at surgery? Is reproductive tissue a special case? Surely, if the eggs were going to be implanted in another woman, one would think that the donor's permission should be obtained. Then what about their simple fertilization? If the woman from whom the eggs are taken has religious or other objections against in vitro fertilization which would lead her to refuse permission if asked, is she wronged by not being asked or informed?<sup>181</sup>

The National Research Council study concurs with Kass's position and adds two further stipulations. First, the semen donor should also give informed consent for the use of his sperm in laboratory studies of IVF. Second, since most potential oocyte donors will be women who are undergoing treatment for infertility, and since basic laboratory research employing their oocytes would be of no direct benefit to them in the relief of their infertility, institutional arrangements should be devised which clearly identify the request for oocyte donation as unrelated to their therapy.<sup>182</sup>

### 3. Macroethical Issues

a. Potential long-term consequences of basic research with early human embryos. Three types of potential consequences have been identified by various commentators: positive, negative, and ambiguous consequences. The National Research Council's assessment of in vitro fertilization provides a summary of the hoped-for positive consequences of basic IVF research:



Experimentation with human eggs, zygotes, blastocysts, and embryos would produce a better understanding of the mechanisms and regulation of embryonic and fetal development, both normal and abnormal....Eventually, knowledge of the pathogenesis of genetic and developmental abnormalities might provide the basis for their prevention or treatment. Experiments with human eggs and embryos also promise greater knowledge of the physiology of pregnancy, especially of factors governing implantation and other fetal-maternal interactions, and, in addition, perhaps the discovery of safer and more effective means of birth control. Laboratory embryos may also some day be useful for assisting in learning about the mutagenic and teratogenic hazards of new drugs and chemicals. Finally, embryo research might help to refine and extend recent discoveries of the importance of prenatal nutrition, and of the prenatal environment in general, for subsequent normal development and maturation.<sup>183</sup>

To this list, James Watson would probably add that cell fusion research with human embryos may provide a useful avenue to understanding "the genetic basis of cancer."<sup>184</sup>

One potential negative consequence of research involving the discard of early embryos has been identified by Leon Kass. In his view, one should "be concerned about the effects on the attitude toward and respect for human life engendered in persons who are engaged in such practices."<sup>185</sup> James Watson expresses disapproval of a second potential consequence of basic IVF research: "...One of the experiments people might try is cloning -- and I think would probably be a bad idea from the start!"<sup>186</sup> R. G. Edwards argues that "some of the consequences judged to be acceptable (with tongue-in-cheek?) such as man/animal hybrids (Fletcher, 1972), are questionable even on 'consequentialist' grounds, for the human component would be condemned to a situation unworthy of it."<sup>187</sup>

However, even on the issues of cloning and human-animal hybrids the commentators diverge in their assessments.<sup>188</sup> Thus, these consequences must perhaps be categorized as ambiguous rather than negative. Similarly dis-

cordant opinions concerning ectogenesis, or extracorporeal gestation, have been expressed.<sup>189</sup> Several of these potential negative and ambiguous consequences will be discussed in greater detail in the second part of this review.

b. Appropriate allocation of resources to basic research with early human embryos and to other areas of research or health care. This issue has received virtually no discussion in the ethical literature on basic IVF research. James Watson does note in passing that experimental work with human embryos is not likely to be outlawed because of its potential value to cancer research and the control of fertility.<sup>190</sup>

This issue is raised in this review chiefly to signal the multiple approaches which can be taken in the ethical evaluation of basic research. As historian Loren Graham suggests, one can examine the treatment of human subjects (the moral-status question), the potential technological and non-technological consequences of basic research, or the allocation of resources to various types of research.<sup>191</sup>

c. Freedom of inquiry and the development of appropriate institutional frameworks for the monitoring of basic research with early human embryos. This final question about basic research again has received relatively little attention in the ethical literature. James Watson, because of his concern about cloning research, has advocated legislation and institutional agreements to control (but not necessarily to prohibit) laboratory research with human oocytes and embryos.<sup>192</sup> In contrast, R. G. Edwards favors a laissez-faire approach by government and self-regulation by physicians and scientists. Speaking on behalf of himself and his research colleagues, Edwards writes, "We believe it essential to pursue research into aspects

of knowledge that could contribute to the well-being of humanity provided the rights of the patients, including those of the foetus, are safeguarded as far as possible."<sup>193</sup>

In the United States a procedural approach has been adopted for the review of both clinical and basic IVF research funded by the Department of Health, Education, and Welfare. While earlier drafts of DHEW guidelines concerning basic research with early human embryos contained either specific stipulations or general criteria for review, the current regulations require only that the Ethics Advisory Board review each application or proposal involving human in vitro fertilization and "[render] advice as to its acceptability from an ethical standpoint."<sup>194</sup>

Although he does not explicitly discuss IVF research, Loren Graham presents a general typology of alternative approaches to the social control of research which may be relevant to basic research with early human embryos, as well:

Possible answers to the question, "At what level should controls be imposed?" include the following levels:

1. The individual researcher
2. The laboratory, university, or industry
3. Funding
  - a. Government support
  - b. Private support
4. Construction of research facilities
5. Actual performance of research
6. Publication of results
7. Application
8. Production
9. Sales
10. Use

Possible answers to the question "Who should establish and administer the controls?" include:

1. The individual researcher
2. The research laboratory, university, or industry
  - a. Government
  - b. Private
3. A group of researchers in the field
4. An established professional organization

5. Mixed boards of specialists and lay people
6. Established governmental bodies
  - a. Local, state or federal
  - b. By means of guidelines or by normal legislation.<sup>196</sup>

## II. Future Issues

In this second part of the review, ethical issues in basic research will be discussed first, since both the research and its applications are future and since the applications will be based directly on the research.

### A. Basic Research

Projections concerning future types of basic research involving human embryos are based on extrapolation from current embryological research with non-human mammals.<sup>197</sup> Research procedures of potential applicability to human embryos can be divided into three categories:

1. Procedures which will probably not be proposed for research with human embryos
2. Research involving oocytes or early stages of embryonic development
3. Research involving later embryos, i.e., embryos which have developed beyond the point at which implantation normally occurs.

#### 1. Procedures Which Will Probably Not Be Proposed for Research with Human Embryos

There are two standard types of research with non-human mammalian embryos which can be noted only in passing since they will probably not be proposed or performed with humans. The first involves the removal, or explanting, of embryos from the uterus following implantation.<sup>198</sup> The second type of research involves the exposure of the implanted embryo either directly or indirectly to potential teratogens or mutagens. Such exposure is followed by the removal of the embryo or subsequent fetus from the uterus, in order to study exposure effects.<sup>199</sup>



These two types of research can be approached either from a definitional or an ethical standpoint. As noted above, the National Commission defined fetus as "the human from the time of implantation until...delivery."<sup>200</sup> The current DHEW guidelines on research with fetuses, pregnant women, and in vitro fertilization accept the Commission's definition with the minor amendment of substituting "product of conception" for "human."<sup>201</sup> Thus, depending upon one's definition of "embryo" and "fetus," these two types of research might or might not be considered research with human embryos.

Ethical issues to be considered in proposals to initiate such research in humans would include: (1) risks to the pregnant woman, particularly in the explantation process; (2) the possibility of the pregnant woman's changing her mind about abortion following the exposure of the "embryo" or fetus to potentially damaging radiation or pharmaceuticals; and (3) the moral status of the postimplantation "embryo" or fetus.<sup>202</sup>

## 2. Research Involving Oocytes or Early Stages of Embryonic Development

At least three lines of investigation in the pre-fertilization and early post-fertilization stages of human development may require ethical analysis: (1) research on parthenogenesis; (2) research on cloning; and (3) research on various types of hybridization or chimera-production. None of these three types of research has received extensive ethical discussion at the basic research level.

a. Research on parthenogenesis. Through electrical or chemical manipulation it is possible to induce the unfertilized oocytes of several mammals -- as well as those of several marine invertebrates and amphibians -- to become activated and to undergo cell division. No fertilization by the male of the species is required to initiate this early "embryonic" develop-

ment. To date, the longest surviving simple parthenogenetic "embryo" was a mouse which lived for ten days, approximately the half-way point in mouse gestation. In studies conducted by Andrzej Tarkowski, only thirty percent of activated mouse oocytes developed far enough to implant.<sup>203</sup>

Two primary rationales for the study of parthenogenesis have been advanced. First, such studies may be useful in investigating the contribution of the sperm to early embryonic development. Second, since parthenogenones are either haploid or homozygously diploid, all mutations are expressed and can be easily identified. Research on spontaneous or induced mutations can therefore be conducted more efficiently in such early "embryos."

The primary question to be raised concerning parthenogenetic research with human ova is: What is the moral status of the early parthenogenone? One quandary to be faced is that traditional views concerning the point at which human life should receive protection have assumed fertilization as a minimum prerequisite. It seems likely, however, that the question of the moral status of human parthenogenones will be ignored unless and until more advanced stages of embryonic and fetal development can be attained.

b. Research on cloning. In its simplest form, cloning involves enucleation of an ovum and the insertion into the ovum of a diploid somatic-cell nucleus. If the experiment is successful-- as in the research with frogs by Robert Briggs, Thomas King, and J. B. Gurdon -- the ovum "accepts" the new nucleus and embryonic development begins. No successful transfer of a body-cell nucleus into an enucleated mammalian egg has been reported in the scientific literature.<sup>204</sup>

The primary rationale for laboratory research with cloning is that it provides information concerning the interaction between the nucleus and the

surrounding cytoplasm of a cell. More specifically, the process by which genes are activated and inactivated can be studied. Knowledge about this process might, in turn, provide important clues in the search for causes of malignant growth.<sup>205</sup>

Most published discussions of ethical issues in cloning have focused on the possible effects of the technique on offspring which might be produced. For mammals, the ethical questions are currently academic. If the successful growth of early human embryos after nuclear transfer is achieved, the nuclear transfer procedure will probably be regarded as the functional equivalent of the fertilization process. If so, the ethical issues in basic research with cloned early human embryos will parallel precisely those raised by research with embryos produced by the in vitro union of sperm and ova.

c. Research on various types of hybridization or chimera-production  
Mammalian hybrids can be created in the laboratory by means of several techniques:

1. Cross-fertilization between different species, e.g., through the combination of human sperm and hamster ova.<sup>206</sup>
2. The fusion of somatic cells with ova.<sup>207</sup>
3. The production of chimeras, either by the injection of cells from one embryo into another or by the fusion of two or more embryos.
  - a. Combination of parthenogenetic "embryos" with embryos produced by fertilization<sup>208</sup>
  - b. Combination of multiple embryos belonging to the same species<sup>209</sup>
  - c. Combination of multiple embryos belonging to different species.<sup>210</sup>

The scientific justification for the production of such hybrids is that the research will provide information about the genetic interplay between or among various cell lines and thus shed light on organ formation and the masking of genetic defects.<sup>211</sup>

Ethical discussion of hybridization as a basic research technique has not occurred. When such discussion does take place, it is likely that a fundamental distinction will be made between research involving only human cells and research involving the combination of human and non-human cells. The fusion of human somatic cells with human ova seems analogous to the nuclear transfer experiments described above and will probably raise few questions at the early embryonic stage of development. The fusion of human parthenogenones with embryos may also occasion little debate, since the moral status of parthenogenones is uncertain. However, questions of individual identity may be considered more important in the deliberate fusion, in whole or in part, of multiple early human embryos. The most controversial type of hybridization research from an ethical standpoint is likely to be that which combines human and non-human mammalian cells--whether gametes or embryonic cells. The moral status of human-animal hybrids, even at this early stage of development, is a matter which will require further philosophical and ethical exploration.

3. Research Involving Later Embryos, i.e., Embryos Which Have Developed Beyond the Point at Which Implantation Normally Occurs

If one extrapolates from basic research currently being conducted with non-human animal species, it seems likely that any attempts to prolong the lives of human embryos (including clones) or hybrids derived in part from human embryos will adopt one of two approaches: (1) embryos will be cultured in vitro; or (2) human-animal hybrids will be transferred to the uterus of a member of the animal species to which the human embryos have been hybridized.

Initial attempts to culture human or hybrid embryos in vitro would



probably not be successful past the stage at which the placenta forms. Until now, all efforts to simulate placental function in vitro in research with mammalian embryos have failed.<sup>212</sup> Similarly, the transfer of hybrid embryos to host mothers has not as yet produced viable offspring and thus in the early phases of human research would probably sustain embryonic and fetal life only for a limited time.<sup>213</sup> Refinements in research procedure may eventually make technically possible the support of human or human-animal fetuses to the stage of viability.

The general rationale for prolonging the lives of human or hybrid embryos and fetuses in the laboratory is that the research would provide detailed information about stages of human development which are normally not accessible for observation. Normal and abnormal organogenesis could be studied, particularly in vitro. In hybrid embryos and fetuses the distinctive contribution of each component could be analyzed. New insights concerning the implantation process (or the prevention thereof) and maternal-fetal interactions might also result from the research.<sup>214</sup>

A major concern in the initial draft of DHEW rules for in vitro fertilization was that no laboratory research accidentally produce a viable fetus. In the words of the draft, "Care must be taken not to bring human ova fertilized in vitro to viability...in the laboratory."<sup>215</sup> This stipulation suggests that if this line of research were successful, difficult decisions would face investigators concerning whether to sustain or terminate the lives of human or hybrid fetuses approaching viability.

The moral status of later human embryos and fetuses would perhaps be the central ethical issue to be faced. As. R. G. Edwards observes, "Growth

of embryos even through the early host-implantation stages will raise some ethical problems, because the fetuses will almost certainly undergo considerable growth and development of various organs."<sup>216</sup> The moral status of embryonic and fetal human-animal hybrids would also be a matter for ethical debate.

In addition, an equal-protection issue may be raised. A human embryo or fetus implanted in the human uterus is currently covered by research guidelines recommended by the National Commission and adopted by DHEW. The nonviable aborted fetus is also afforded certain protections by the same set of guidelines.<sup>217</sup> Would such guidelines also apply to human embryos and fetuses of the same gestational age which were "implanted" in vitro rather than in the human uterus? Would the same or similar guidelines apply to human-animal hybrids cultured in vitro past the implantation stage or indeed implanted in the uteri of non-human mammals?

#### B. Clinical and Technological Applications

Commentators on ethical issues in IVF and embryo transfer have devoted substantially greater attention to future potential applications of the techniques than to basic-research questions. At least six distinct applications have been identified:

1. The sexing of embryos
2. Preimplantational genetic screening
3. The preimplantational repair of genetic defects
4. The creation of human-animal hybrids
5. Cloning
6. Ectogenesis

Whether one considers each of these applications to be "clinical" or "technological" depends upon one's conception of appropriate health care and one's definition of health.

### 1. The Sexing of Embryos

R.G. Edwards suggests that one of the earliest future applications of research on human IVF and embryo transfer may be the predetermination of embryonic sex.<sup>218</sup> Such parental selection might be based on the desire to avoid a genetic defect in their offspring--for example, an X-linked defect like hemophilia--or simply on a preference for having children of a particular sex in a preselected order.

At least two ethical questions can be raised about the sexing of blastocysts. Edwards notes that one would need to monitor changes in sex ratio quite carefully. Otherwise, a slight excess of males, for example, might lead to the "'raiding' of the younger age-groups of women by older men."<sup>219</sup> Second, the discard-question discussed previously arises again with this potential application. Edwards himself admits that the sexing of sperm would be ethically preferable to the selection of blastocysts on sexual grounds; however, sperm sexing is, in his view, currently infeasible.<sup>220</sup>

### 2. Preimplantational Genetic Screening

A closely related application would examine early embryos for chromosome abnormalities and genetic defects. Bentley Glass,<sup>221</sup> R.G. Edwards and David Sharpe,<sup>222</sup> and Laurence Karp and Roger Donohue<sup>223</sup> expressly advocate this use of human IVF and embryo transfer. While the discard-problem would remain to be considered, most ethical evaluations would probably regard preimplantational genetic screening as preferable to prenatal diagnosis and selective abortion during the mid-trimester of pregnancy.<sup>224</sup>

### 3. The Preimplantational Repair of Genetic Defects

A possible alternative to the discarding of genetically defective early embryos would be the repair of the defects. Robert Sinsheimer suggests that

such repairs might be accomplished through one of three mechanisms: (1) DNA transformation, the uptake of DNA by embryonic cells; (2) DNA transduction via a temperate virus; and (3) chimera formation.<sup>225</sup> R.G. Edwards further subdivides the third alternative into two subtypes: the injection of embryonic cells into the blastocyst and the fusing of multiple embryos.<sup>226</sup>

Potential benefits of these techniques are that they would, if successful, mask genetic defects. In fact, chimera-formation often could be employed to provide a "composite organ transplant" to the early embryo.<sup>227</sup> However, these powerful techniques might profoundly affect brain development, unintentionally convey deleterious genes to the embryonic patient, and--on the macro-level--increase the incidence of genetic defects in the population.<sup>228</sup> R.G. Edwards' most recent verdict on chimera-formation as a method of gene repair is that "there is hardly any point in making chimeras until some clinical advantage can be shown to accrue from the method."<sup>229</sup>

Ethical discussion of gene repair will probably center on the potential risks and benefits of the various techniques and on the alternatives of repair vs. discard of defective early embryos. The combination of elements from multiple human embryos to create a less-afflicted composite may also be debated because of its challenge to prevalent concepts of individual identity.

#### 4. The Creation of Human-Animal Hybrids

This application presupposes that it will one day be possible to continue the development of human-animal hybrids to and beyond the stage of viability. Joseph Fletcher, who has discussed this possibility in perhaps the most detail, suggests both medical and nonmedical reasons for such a creation: (1) medically, herds of man-animal combinations may be raised to provide organs for transplantation; and (2) socially, "Chimeras or para-



humans might legitimately be fashioned to do dangerous or demeaning jobs.<sup>230</sup> In the opinion of R.G. Edwards the proposed creation of human-animal hybrids is ethically questionable because "the human component would be condemned to a situation unworthy of it."<sup>231</sup>

## 5. Cloning

Perhaps no other potential application of IVF and embryo transfer in humans has engendered as much debate as the proposal to clone a human being. Among the ethical objections which have been raised against cloning are: (1) the technique would condemn an offspring to grow up knowing that he or she had the same genetic potential as an identifiable predecessor;<sup>232</sup> (2) the creation of multiple copies of one person would lead to a loss of identity in the offspring;<sup>233</sup> and (3) the technique gives members of the present generation the Promethean power to determine the conditions of future human life.<sup>234</sup>

Other commentators have enumerated several potential benefits of cloning. Joshua Lederberg notes that the technique could be employed to allow anovulatory women or azoospermic men to contribute to the production of children.<sup>235</sup> Joseph Fletcher adds that clones could serve as organ donors for one another and that society might need to reproduce specialized individuals to fulfill unique roles--individuals with special resistance to radiation or small body size and weight, for example, who might be "invaluable for professional flights at high altitudes and space travel."<sup>236</sup> In addition, Fletcher argues, cloning may become a necessary adjunct to human reproduction in human efforts to prevent further deterioration of the gene pool.<sup>237</sup>

R.G. Edwards adopts a mediating position on cloning. He expresses regret that the issue has been given a "false prominence" by scientists and commentators alike. According to Edwards, the technique of cloning may not

be as successful as its proponents claim: somatic mutations could modify the donor nucleus; in addition, there is convincing evidence that the uterine environment strongly affects the phenotype of mammalian offspring. After considering the promised benefits and the potential hazards of cloning, Edwards seems to conclude that the technique of human cloning is, on balance, not needed by the society of today.<sup>238</sup>

#### 6. Ectogenesis

A final potential application of research on human IVF and embryo transfer would be extracorporeal gestation of the human embryo and fetus. Proponents of ectogenesis point to its therapeutic value in saving the lives of premature infants. They also note that extracorporeal gestation would alleviate maternal and fetal morbidity and mortality through the reduction of fetal exposure to teratogens and the elimination of birth trauma.<sup>239</sup>

There has been little explicit discussion of ethical issues in ectogenesis by critics of the technology. Issues deserving consideration might include the safety of the technique and the potential psychological impact on both parents and their offspring of a change from maternal-fetal interaction to machine-based gestation.<sup>240</sup>

### Footnotes

1. U.S., National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, Research on the Fetus: Report and Recommendations and Appendix (Washington, D.C.: Department of Health, Education, and Welfare, 1975).
2. U.S., National Commission, Research on the Fetus: Report and Recommendations, p. 5.
3. The term "early embryo" is employed in preference to "preimplantation embryo" because not all embryos employed in laboratory research on in vitro fertilization are intended to be implanted.
4. The preamble to the current DHEW regulations on fetal research designates such organisms as "the non-implanted product[s] of in vitro fertilization" [DHEW, Office of the Secretary, "Protection of Human Subjects: Fetuses, Pregnant Women, and In Vitro Fertilization (Federal Register 40(154): 33527, 8 August 1975)]. It is not clear from the preamble whether attachment to an artificial placenta or uterus or transfer to the reproductive tract of a non-human mammal would be considered "implantation."
5. Jan Langman, Medical Embryology: Human Development -- Normal and Abnormal (2nd ed.; Baltimore: William and Wilkins, 1969), p. 31.
6. Ruth E. Fowler and R. G. Edwards, "The Genetics of Early Human Development," in Arthur G. Steinberg and Alexander G. Bearn, eds., Progress in Medical Genetics, Vol. IX (New York: Grune and Stratton, 1973), p. 78.
7. This chronology, which is available in any detailed textbook of human embryology, was taken from Keith L. Moore, The Developing Human: Clinically Oriented Embryology (2nd ed.; Philadelphia: W. B. Saunders, 1977), esp. pp. 2-4.
8. The order of prevalence is of course an impressionistic estimate. The estimate does not attempt to adjust for the fact that a few authors have been quite prolific on the ethics of clinical IVF and have done much to establish the agenda for discussion of this topic.
9. Leon R. Kass, "Making Babies -- The New Biology and the 'Old' Morality," Public Interest, No. 26: 32-33, Winter 1972. This essay is a slightly revised version of a paper entitled "New Beginnings in Life," which was presented at a 1971 conference and subsequently published in Michael P. Hamilton, ed., The New Genetics and the Future of Man (Grand Rapids: Eerdmans, 1972), pp. 15-63.
10. André E. Hellegers and Richard A. McCormick, "Unanswered Questions on Test Tube Life," America 139(4): 76, 12-19 August 1978.

11. Paul Ramsey, "Shall We 'Reproduce'? I. The Medical Ethics of In Vitro Fertilization," JAMA 220(10): 1347, 5 June 1972.
12. Alun Jones and Walter F. Bodmer, "Artificial Fertilization," in their Our Future Inheritance: Choice or Chance? A Study by a British Association Working Party (London: Oxford University Press, 1974), p. 44.
13. R. G. Edwards, "Fertilization of Human Eggs in Vitro: Morals, Ethics and the Law," Quarterly Review of Biology 49(1): 13-14, March 1974.
14. Joseph Fletcher, in Gebhard F. Schumacher, et al., "In Vitro Fertilization of Human Ova and Blastocyst Transfer: An Invitational Symposium," Journal of Reproductive Medicine 11(5): 198, November 1972. Cf. Joseph Fletcher, The Ethics of Genetic Control: Ending Reproductive Roulette (Anchor Books; Garden City, N.Y.: Anchor Press/Doubleday, 1974), pp. 92, 94.
15. George V. Lobo, Current Problems in Medical Ethics: A Comprehensive Guide to Ethical Problems in Medical Practice (Allahabad, India: St. Paul Publications, 1974), pp. 103-106, 152-153. For further discussion of estimated rates of human embryonic loss in vivo, see Arthur J. Hertig, et al., "Thirty-Four Fertilized Ova, Good, Bad and Indifferent, Recovered from 210 Women of Known Fertility," Pediatrics 23(1, Pt. II): 202-211, January 1959; cf. William H. James, "The Incidence of Spontaneous Abortion," Population Studies 24(2): 241-245, July 1970. For a critique of the paper by Hertig and associates, see Thomas W. Hilgers, "Human Reproduction: Three Issues for the Moral Theologian," Theological Studies 38(1): 147-149, March 1977.
16. See fn. 12 above.
17. Kass, "Making Babies," p. 49.
18. "Address of His Holiness, Pope Pius XII, to the Second World Congress on Fertility and Sterility," in G. Tesauro, ed., Proceedings of the Second World Congress on Fertility and Sterility [Naples, Italy, May 18-26, 1956] (2 vols.; Naples: Institute of Clinical Obstetrics and Gynecology, University of Naples, 1957-58), I, 40.
19. Ibid., p. 41.
20. Paul Ramsey, "Moral and Religious Implications of Genetic Control," in his Fabricated Man: The Ethics of Genetic Control (New Haven: Yale University Press, 1970), pp. 50-57; Paul Ramsey, "Shall We 'Reproduce'? II. Rejoinders and Future Forecast," JAMA 220(11): 1480-1483, 12 June 1972.
21. Immanuel Jakobovits, Jewish Medical Ethics (2nd ed.; New York: Block Publishing Company, 1975), p. 264.
22. Charles E. Curran, Politics, Medicine, and Christian Ethics: A Dialogue with Paul Ramsey (Philadelphia: Fortress Press, 1973), pp. 212-216.



23. Hellegers and McCormick, "Unanswered Questions," pp. 75-76.
24. Edwards, "Fertilization," p. 14.
25. Daniel Callahan, "New Beginnings in Life: A Philosopher's Response," in Hamilton, ed., The New Genetics (see fn. 9 above), pp. 100-101.
26. Fletcher, The Ethics of Genetic Control, p. 44.
27. Ibid., p. 36. Footnote "a" cites "E. Kal (letter to the editor), Journal of the American Medical Association, 221 (September 18, 1972), 1409."
28. For an attempt to identify and summarize these recurrent themes see LeRoy Walters, "Some Ethical Issues in Research Involving Human Subjects," Perspectives in Biology and Medicine 20(2): 193-211, Winter 1977.
29. Edwards, "Fertilization," p. 10.
30. National Research Council, Assembly of Behavioral and Social Sciences, Committee on the Life Sciences and Social Policy, Assessing Biomedical Technologies: An Inquiry into the Nature of the Process (Washington, D.C.: National Academy of Sciences, 1975), p. 20.
31. Kass, "Making Babies," p. 26.
32. Ramsey, "Shall We 'Reproduce'? II," p. 1481.
33. Edwards, "Fertilization," p. 10.
34. Leon R. Kass, "Babies by Means of In Vitro Fertilization: Unethical Experiments on the Unborn?" New England Journal of Medicine 285(21): 1176-1177, 18 November 1971.
35. Ramsey, "Shall We 'Reproduce'? II," pp. 1481, 1485, fn. 3.
36. Robert G. Edwards and David J. Sharpe, "Social Values and Research in Human Embryology," Nature 231(5298): 87, 14 May 1971.
37. Ibid.
38. Edwards, "Fertilization," p. 11.
39. World Medical Association, "Declaration of Helsinki," Medical Journal of Australia 1(7): 206, 14 February 1976.
40. Kass, "Making Babies," p. 28; cf. Kass, "Babies by Means of In Vitro Fertilization," pp. 1176, 1178.
41. Marc Lappé, "Risk-Taking for the Unborn," Hastings Center Report 2(1): 3, February 1972; cf. Steven Hecht and Marc Lappé, "Moratorium on Human Zygote Implantation [Letter]," New England Journal of Medicine 287(13): 672, 28 September 1972.

42. B. G. Brackett, in Schumacher, et al., "In Vitro Fertilization" (see fn. 14 above), p. 144.
43. Luigi Mastroianni, "Fertilization and the Tubal Environment," Hospital Practice 7(3): 118, March 1972.
44. Benjamin G. Brackett, "Comment on Human Fertilization in Vitro...", statement before the Subcommittee on Health and the Environment, House Committee on Interstate and Foreign Commerce, 4 August 1978, 5 pp., unpublished.
45. Ibid., p. 3.
46. Kass, "Making Babies," p. 28; Lappé, "Risk-Taking," p. 3.
47. Brackett, "Comment," pp. 3-4.
48. National Research Council, Assessing Biomedical Technologies, p. 18.
49. L. B. Shettles, in Schumacher, et al., "In Vitro Fertilization" (see fn. 14 above), p. 197.
50. Edwards, "Fertilization," pp. 8-9.
51. U.S., DHEW, National Institutes of Health, "Protection of Human Subjects: Policies and Procedures," Federal Register 38(221): 31743, 16 November 1973.
52. U.S., DHEW, Office of the Secretary, "Protection of Human Subjects: Proposed Policy," Federal Register 39(165): 30650, 23 August 1974.
53. The reason for presenting opponents' arguments first and proponents' arguments second in most sections is that the opponents' most comprehensive statements of their positions predated the proponents' most detailed statements of theirs. Proponents of clinical IVF research are therefore able to reply to some arguments presented by the opponents. Little surrebuttal by the opponents of clinical IVF research has occurred.
54. Edwards, "Fertilization," pp. 8-9.
55. Shettles, in Schumacher, et al., "In Vitro Fertilization" (see fn. 14 above), pp. 196-197.
56. Jones and Bodmer, Our Future Inheritance, pp. 36-38.
57. Kass, "Making Babies," pp. 27-28; Kass, "Babies by Means of In Vitro Fertilization," pp. 1175-1176.
58. Mastroianni, in Schumacher, et al., "In Vitro Fertilization" (see fn. 14 above), pp. 196, 199.

59. Brackett, Ibid.
60. Lappé, "Risk-Taking for the Unborn," p. 3.
61. National Research Council, Assessing Biomedical Technologies, p. 18.
62. Jakobovits, Jewish Medical Ethics, 2nd ed., p. 266. Jakobovits cites "the recent history of heart-transplants, and the indecent haste with which doctors and hospitals competed in these premature operations at the cost of scores of lives and the false hopes raised and tragically dashed in millions of sufferers."
63. Kass, "Making Babies," p. 28; Kass, "Babies by Means of In Vitro Fertilization," p. 1176.
64. Ramsey, "Shall We 'Reproduce'? I," p. 1348.
65. National Research Council, Assessing Biomedical Technologies, p. 18.
66. Ramsey, "Shall We 'Reproduce'? I," pp. 1347-1348; cf. Ramsey, Fabricated Man, p. 113.
67. Kass, "Making Babies," pp. 29-30.
68. Fletcher, The Ethics of Genetic Control, pp. 93-94.
69. Ibid., pp. 93-96, 103, 166; cf. Fletcher, in Schumacher, et al., "In Vitro Fertilization" (see fn. 14 above), p. 199.
70. Lappé, "Risk-Taking for the Unborn," p. 2.
71. Curran, Politics, Medicine, and Christian Ethics, p. 215.
72. James D. Watson, "Children from the Laboratory," Prism [AMA] 1(2): 13, May 1973.
73. Edwards, "Fertilization," p. 9.
74. Ramsey, "Shall We 'Reproduce'? I," p. 1349.
75. Kass ("Babies by Means of In Vitro Fertilization," p. 1177), Ramsey, ("Shall We 'Reproduce'? I," pp. 1349-1350), and Edwards ("Fertilization," p. 16) allude to this philosophical and legal problem without discussing it in detail.
76. In this section the oocyte donor is also the recipient of the early embryo, i.e., the would-be host mother.
77. Luigi Mastroianni, Jr., "Reproductive Interventions: IV. In Vitro Fertilization," Encyclopedia of Bioethics (4 vols.; New York: Free Press-MacMillan, in press).

78. Jones and Bodmer, Our Future Inheritance, pp. 33-34.
79. Edwards, "Fertilization," p. 8.
80. Ramsey, "Shall We 'Reproduce'? I," p. 1349.
81. P. C. Steptoe and R. G. Edwards, "Reimplantation of a Human Embryo with Subsequent Tubal Pregnancy," Lancet 1(7965): 880-882, 24 April 1976.
82. National Research Council, Assessing Biomedical Technologies, pp. 17-18.
83. Edwards, "Fertilization," p. 8.
84. Mastroianni, "Reproductive Interventions" (see fn. 77 above).
85. See, for example, Fletcher, The Ethics of Genetic Control, p. 93; Kass, "Making Babies," pp. 30-31; Edwards, "Fertilization," p. 11; British Medical Association, Board of Science and Education, Special Panel, Professional Standards (London: British Medical Association, March 1972), pp. 9-10.
86. Kass, "Making Babies," p. 31.
87. Items (2) through (4) are enumerated in National Research Council, Assessing Biomedical Technologies, p. 21.
88. British Medical Association, Professional Standards, p. 10.
89. National Research Council, Assessing Biomedical Technologies, pp. 21, 27.
90. Mastroianni, in Schumacher, et al., "In Vitro Fertilization" (see fn. 14 above), p. 197; National Research Council, Assessing Biomedical Technologies, p. 21.
91. National Research Council, Assessing Biomedical Technologies, pp. 23, 27.
92. Edwards, "Fertilization," p. 11.
93. Kass, "Making Babies," pp. 29-30; cf. Kass, "Babies by Means of In Vitro Fertilization," p. 1176.
94. Ramsey, "Shall We 'Reproduce'? I," p. 1349.
94. For a parallel discussion of risk and consent in nontherapeutic research involving children, see Paul Ramsey, The Patient as Person: Exploration in Medical Ethics (New Haven: Yale University Press, 1970), esp. pp. 39-40.
96. Fletcher, The Ethics of Genetic Control, pp. 94-95; Edwards, "Fertilization," p. 14.
97. Edwards, "Fertilization," p. 14.



98. Jakobovits, Jewish Medical Ethics, 2nd ed., p. 266.
99. Lappé, "Risk-Taking for the Unborn," p. 2.
100. Lord Kilbrandon, in "Discussion: Legal Aspects," in Law and Ethics of A.I.D. and Embryo Transfer (Amsterdam: Associated Scientific Publishers, 1973), p. 93.
101. R. G. Edwards, ibid.
102. R. G. Edwards, ibid., p. 94.
103. Lappé, "Risk-Taking for the Unborn," p. 3; Kass, "Babies by Means of In Vitro Fertilization," p. 1176.
104. Angela Roddey Holder, Legal Issues in Pediatrics and Adolescent Medicine (New York: John Wiley and Sons, 1977), p. 24.
105. [Report of the] HEW Secretary's Task Force on the Compensation of Injured Research Subjects (3 vols.; Washington, D.C.: DHEW, Office of the Secretary, January 1977), Vol. I, p. VI-9.
106. R. G. Edwards notes, for example, that genetic defects which had not been expressed in the parent could be expressed in their child ("Fertilization," p. 17).
107. Edwards, "Fertilization," p. 18.
108. R. G. Edwards suggests that if the IVF or embryo transfer had been negligently performed and had therefore resulted in deformity to the child, a plaintiff might be justified in claiming damages for the difference between a normal and a deformed child (Edwards, "Fertilization," p. 17).
109. National Research Council, Assessing Biomedical Technologies, pp. 23-26.
110. Ibid., p. 26
111. Ibid., pp. 23-24; Fletcher, The Ethics of Genetic Control, p. 70.
112. Edwards and Sharpe, "Social Values," p. 88; Edwards, "Fertilization," p. 12; Watson, "Children from the Laboratory," p. 14.
113. Bentley Glass, "Science: Endless Horizons or Golden Age?" Science 171(3966): 28, 8 January 1971; British Medical Association, Professional Standards, p. 10; Laurence E. Karp and Roger P. Donahue, "Preimplantational Ectogenesis: Science and Speculation Concerning In Vitro Fertilization and Related Procedures," Western Journal of Medicine 124(4): 295, April 1976.
114. Edwards and Sharpe, "Social Values," p. 88; Edwards, "Fertilization," pp. 9-10, 12.

115. Robert L. Sinsheimer, "Prospects for Future Scientific Developments: Ambush or Opportunity," in Bruce Hilton, et al, eds. Ethical Issues in Human Genetics: Genetic Counseling and the Use of Genetic Knowledge (New York: Plenum Press, 1973), pp. 346-348.
116. James D. Watson, Statement at the Twelfth Meeting of the Panel on Science and Technology, International Science Policy, Proceedings before the Committee on Science and Astronautics, U.S. House of Representatives, 92nd Congress, 1st Session, January 26, 27, and 28, 1971 (Washington, D.C.: U.S. Government Printing Office, 1971), p. 342; Edwards and Sharpe, "Social Values," pp. 88-89; Fletcher, The Ethics of Genetic Control, pp. 71-76; Edwards, "Fertilization," pp. 12-13.
117. Paul Ramsey, "Shall We 'Reproduce'? I," p. 1481; "Genetic Engineering: Reprise [Editorial]," JAMA 220(10): 1356, 5 June 1972; Edwards, "Fertilization," p. 12.
118. "Genetic Engineering: Reprise [Editorial]," p. 1356; Kass, "Babies by Means of In Vitro Fertilization," p. 1178; Fletcher, The Ethics of Genetic Control, pp. 163-165.
119. Watson, Statement (see fn. 116 above), p. 143.
120. G. R. Dunstan, The Artifice of Ethics (London: SCM Press, 1974), p. 60.
121. Kass, "Babies by Means of In Vitro Fertilization," p. 1178; cf. Ramsey, "Shall We 'Reproduce'? II," p. 1481,
122. Fletcher, The Ethics of Genetic Control, pp. 86, 164; Glass, "Science: Endless Horizon or Golden Age?," p. 28.
123. Edwards, "Fertilization," pp. 12-13.
124. National Research Council, Assessing Biomedical Technologies, p. 23.
125. Hellegers and McCormick, "Unanswered Questions," p. 77.
126. Ibid., p. 78.
127. Edwards, "Fertilization," p. 10.
128. Watson, Statement (see fn. 116 above), p. 344.
129. Kass, "Babies by Means of In Vitro Fertilization," p. 1178.
130. Lappé, "Risk-Taking for the Unborn," p. 3.
131. Edwards and Sharpe, "Social Values," p. 40.
132. "Rules and Regulations for Test-Tube Babies [Editorial]," Nature 231(5298): 70, 14 May 1971.

133. Library of Congress, Congressional Research Service, Science Policy Research Division, Genetic Engineering: Evolution of a Technological Issue, Report to the Subcommittee on Science and Astronautics, U.S. House of Representatives, 92nd Congress, 2nd Session, November 1972 (Washington, D.C.: U.S. Government Printing Office, 1972), p. 40. This report was written by Dr. James M. McCullough.
134. Watson, "Children from the Laboratory," pp. 14, 33, and 34.
135. Fletcher, The Ethics of Genetic Control, p. 26.
136. Jakobovits, Jewish Medical Ethics, 2nd ed., pp. 264-265.
137. Kass, "Babies by Means of In Vitro Fertilization," p. 1178.
138. Lappé, "Risk-Taking for the Unborn," p. 3; cf. Hecht and Lappé, "Moratorium on Human Zygote Implantation," p. 672.
139. "Genetic Engineering in Man: Ethical Considerations [Editorial]," JAMA 220(5): 721, 1 May 1972.
140. Federal Register 38(221): 31743, 16 November 1973.
141. Federal Register 39(165): 30650, 23 August 1974.
142. Federal Register 40(154): 33527, 33529, 8 August 1975.
143. Ibid., p. 33529.
144. A second example, not discussed extensively in the literature and omitted from this review, would be the "adoption," by a couple in which both members lack gametes, of an early embryo produced by a combination of a donor oocyte and donor sperm.
145. National Research Council, Assessing Biomedical Technologies, pp. 23-24.
146. Jakobovits, Jewish Medical Ethics, 2nd ed., pp. 264-265.
147. Bernard Häring, Ethics of Manipulation: Issues in Medicine, Behavior Control, and Genetics (New York: Seabury Press, 1975) pp. 196-200.
148. Ramsey, Fabricated Man, p. 107.
149. National Research Council, Assessing Biomedical Technologies, p. 24.
150. Fletcher, The Ethics of Genetic Control, p. 165.
151. Edwards, "Fertilization," p. 10.
152. National Research Council, Assessing Biomedical Technologies, p. 26; Philip Reilly, "In Vitro Fertilization -- a Legal Perspective," in Aubrey Milunsky and George J. Annas, eds. Genetics and the Law (New York: Plenum Press, 1975), p. 370.

153. Holder, Legal Issues in Pediatrics and Adolescent Medicine, pp. 7-9.
154. Reilly, "In Vitro Fertilization," pp. 371-373.
155. Ibid.
156. Karp and Donahue, "Preimplantational Ectogenesis," p. 295.
157. Kass, "Making Babies," p. 36; Watson, "Children from the Laboratory," p. 14.
158. Edwards, "Fertilization," p. 12.
159. Watson, Statement (see fn. 116 above), p. 342.
160. British Medical Association, Professional Standards, p. 10.
161. Jakobovits, Jewish Medical Ethics, 2nd ed., p. 265.
162. Häring, Ethics of Manipulation, pp. 200-201.
163. Ramsey, Fabricated Man, p. 107.
164. Kass, "Making Babies," pp. 35-38.
165. Fletcher, The Ethics of Genetic Control, p. 163.
166. Karp and Donahue, "Preimplantational Ectogenesis," p. 295.
167. Mariel Revillard, "Legal Aspects of Artificial Insemination and Embryo Transfer in French Domestic Law and Private International Law," in Law and Ethics of A.I.D. and Embryo Transfer (see fn. 100 above), p. 87.
168. Reilly, "In Vitro Fertilization," pp. 370-373.
169. Fowler and Edwards, "The Genetics of Early Human Development" (see fn. 6 above), pp. 92-95; Karp and Donahue, "Preimplantational Ectogenesis," p. 296; National Research Council, Assessing Biomedical Technologies, p. 27.
170. Culture of human embryos beyond the blastocyst stage has not yet been reported in the scientific literature.
171. The use of several of these techniques in research with non-human embryos is described by Edwards, "Fertilization," pp. 3-6.
172. Karl Rahner, Theological Investigations, Vol. IX: Writings of 1965-67, I, translated by Graham Harrison (New York: Herder and Herder, 1972), p. 227.
173. Ibid., p. 236.
174. Dunstan, The Artifice of Ethics, pp. 66-73.



175. Kass, "Making Babies," pp. 32-33; cf. National Research Council, Assessing Biomedical Technologies, pp. 27-28.
176. Haring, Ethics of Manipulation, pp. 198-199.
177. DHEW, Office of the Secretary, "Protection of Human Subjects: Proposed Policy," Federal Register 39(165): 30650, 23 August 1974.
178. Mastroianni, "Reproductive Interventions" (see fn. 77 above).
179. U.S., National Commission, Research on the Fetus: Report and Recommendations, p. 74.
180. R. G. Edwards, "Aspects of Human Reproduction," in Watson Fuller, ed., The Biological Revolution: Social Good or Social Evil? (Anchor Books; Garden City, N.Y.: Doubleday and Company, 1972), pp. 133-134. This book was originally published under the title The Social Impact of Modern Biology by Routledge and Kegan Paul Ltd., London, in 1971.
181. Kass, "Making Babies," pp. 31-32.
182. National Research Council, Assessing Biomedical Technologies, p. 27.
183. Ibid.
184. Watson, Statement (see fn. 116 above), p. 343.
185. Kass, "Making Babies," p. 33.
186. Watson, "Children from the Laboratory," p. 13.
187. Edwards, "Fertilization," p. 15; the reference in parentheses is to "Fletcher, J. 1971a. Ethical aspects of genetic controls. New England Journal of Medicine, 285: 776-783."
188. Edwards, "Fertilization," pp. 12-13; Fletcher, The Ethics of Genetic Control, pp. 154-156, 171-173.
189. Fletcher, ibid., pp. 163-165; National Research Council, Assessing Biomedical Technologies, p. 28; Ramsey, Fabricated Man, pp. 113-114.
190. Watson, Statement (see fn. 116 above), p. 343.
191. Loren R. Graham, "Concerns about Science and Attempts to Regulate Inquiry," in Daedalus 107(2): 2-3, Spring 1978 (special issue of Daedalus on "Limits of Scientific Inquiry").
192. Watson, "Children from the Laboratory," pp. 14, 33.
193. Edwards, "Aspects of Human Reproduction," p. 136; cf. Edwards and Sharpe, "Social Values," pp. 89-90.

195. DHEW, Office of the Secretary, "Protection of Human Subjects: Fetuses, Pregnant Women, and In Vitro Fertilization," Federal Register 40(154): 33529, 8 August 1975.
196. Graham, "Concerns about Science," p. 18.
197. For an overview of such research, see C. R. Austin, ed., The Mammalian Fetus in vitro (London: Chapman and Hall, 1973).
198. D. A. J. New, "Studies of Mammalian Fetuses in vitro during the Period of Organogenesis," in C. R. Austin, ed., The Mammalian Fetus in vitro, pp. 15-65.
199. The preclinical testing of drugs for possible teratogenicity in animal models is an example of this second type of research.
200. See fn. 2 above.
201. DHEW, Office of the Secretary, "Protection of Human Subjects: Fetuses, Pregnant Women, and In Vitro Fertilization," Federal Register 40(154): 33529, 8 August 1975.
202. For detailed discussions of issues (2) and (3) see U.S., National Commission, Research on the Fetus: Report and Recommendations, passim; Great Britain, Advisory Group, The Use of Fetuses and Fetal Material for Research (London: Her Majesty's Stationary Office, 1972).
203. Laurence E. Karp, Genetic Engineering: Threat or Promise? (Chicago: Nelson-Hall, 1976), pp. 186-188.
204. Ibid., p. 200.
205. Ibid., pp. 201-203.
206. R. Yanagimachi, H. Yanagimachi, and B. J. Rogers, "The Use of Zona-Free Ova as a Test-System for the Assessment of the Fertilizing Capacity of Human Spermatozoa," Biology of Reproduction 15(4): 471-476, November 1976; M. C. Chang and J. L. Hancock, "Experimental Hybridization," in Kurt Benirschke, ed., Comparative Aspects of Reproductive Failure (New York: Springer-Verlag, 1967), pp. 206-217.
207. Christopher F. Graham, "The Fusion of Cells with One- and Two-Cell Mouse Embryos," in Vittorio Defendi, ed., Heterospecific Genome Interaction, Wistar Institute Symposium Monograph No. 9 (Philadelphia: Wistar Institute Press, 1969), pp. 19-33.
208. Leroy C. Stevens, Don S. Varnum, and Eva M. Eicher, "Viable Chimeras Produced from Normal and Parthenogenetic Mouse Embryos," Nature 269 (5628): 515-517, 6 October 1977.
209. Edwards, "Fertilization," p. 6.

210. G. H. Zeilmaker, "Fusion of Rat and Mouse Morulae and Formation of Chimaeric Blastocysts," Nature 242(5393): 115-116, 9 March 1973; A. J. Copp and J. Rossant, "Effect of Implantational Delay on Transfer of Rat Embryos to Mice," Journal of Reproduction and Fertility 52(1): 119-121, January 1978.
211. Edwards, "Fertilization," p. 6; Edwards and Sharp, "Social Values," p. 88.
212. New, "Studies in Mammalian Fetuses in vitro during the Period of Organogenesis," p. 56.
213. Copp and Rossant, "Effect of Implantational Delay on Transfer of Rat Embryos to Mice," p. 119.
214. Edwards, "Aspects of Human Reproduction," p. 132; Karp, Genetic Engineering, p. 179.
215. DHEW, National Institutes of Health, "Protection of Human Subjects: Policies and Procedures," Federal Register 38(221): 31743, 16 November 1973.
216. Edwards, "Aspects of Human Reproduction," pp. 132-133.
217. U.S. National Commission, Research on the Fetus: Report and Recommendations, p. 74.
218. Edwards, "Fertilization," p. 12; cf. Edwards and Sharpe, "Social Values," p. 88.
219. Edwards and Sharpe, "Social Values," p. 88.
220. Edwards, "Aspects of Human Reproduction," p. 131.
221. Glass, "Science: Endless Horizons or Golden Age?" p. 28.
222. Edwards and Sharpe, "Social Values," p. 88.
223. Karp and Donahue, "Preimplantational Ectogenesis," p. 295.
224. Ibid.
225. Sinsheimer, "Prospects for Future Scientific Developments" (see fn. 115 above), pp. 346-348.
226. Edwards, "Fertilization," p. 6.
227. Edwards and Sharpe, "Social Values," p. 88.
228. Edwards, "Aspects of Human Reproduction," pp. 136-137.
229. Edwards, "Fertilization," p. 12.
230. Fletcher, The Ethics of Genetic Control, pp. 172-173.

- 231. Edwards, "Fertilization," p. 15.
- 232. Watson, "Children from the Laboratory," p. 13.
- 233. Kass, "Making Babies," p. 43.
- 234. Ramsey, Fabricated Man, pp. 94-95.
- 235. Joshua Lederberg, "Biological Innovation and Genetic Intervention," in John A. Behnke, ed., Challenging Biomedical Problems: Directions toward Their Solution (New York: Oxford University Press, 1972), p. 23.
- 236. Fletcher, The Ethics of Genetic Control, p. 155.
- 237. Ibid.
- 238. Edwards, "Fertilization," pp. 12-13.
- 239. Karp, Genetic Engineering, pp. 179-180; cf. Fletcher, The Ethics of Genetic Control, pp. 164-165.
- 240. Häring, Ethics of Manipulation, p. 202; Kass, "Making Babies," pp. 48-49.



ETHICAL ISSUES IN HUMAN IN VITRO FERTILIZATION,  
EMBRYO CULTURE AND RESEARCH, AND EMBRYO TRANSFER

Leon R. Kass, M.D., Ph.D.



Ethical Issues in Human In Vitro Fertilization,  
Embryo Culture and Research, and Embryo Transfer<sup>1</sup>

Leon R. Kass, M.D., Ph.D.

Thank you very much for offering me the opportunity to contribute to the deliberations of the Ethics Advisory Board. As you know, I have long been concerned about the implications of novel laboratory interventions into human reproduction. My earlier writings on this subject, designed mainly to promote serious discussion of the ethical issues, have earned me, not altogether undeservedly the reputation of being an opponent of all such interventions. LeRoy Walters has ably and largely accurately dissected my writings in his survey essay,<sup>2</sup> allocating the various points I have made under his precise analytic schema, although this procedure has deprived the argument of its cumulative weight. Indeed, there is a latent danger of overlooking the forest for the trees in the otherwise rational procedure of considering the issues one at a time. Because I think the intact argument bears your consideration, and because there would be no point to say again what is already published, I am taking the liberty of appending my "Making Babies" article<sup>3</sup> to this paper, despite the fact that my views on the matter are no longer exactly what they were. My intuitions and thoughts about the wisdom of proceeding with this research are still on balance the same and negative, though less intensely so. I cannot decide whether the decline in my passion is to be welcomed; that is, whether it is due to greater understanding bred of more thought and experience or to greater callousness or the contempt of familiarity bred from too much thought and experience. Further, my earlier writing preceded the Supreme Court's decision on abortion, the controversy about fetal research, and many overt changes in our public speech and behavior regarding the meaning of gender, sexuality, procreation, family life, and so on. It seems to me now that the fundamental values that might be challenged by laboratory growth of human embryos and by laboratory assisted reproduction are already severely challenged in perhaps more potent and important ways. Finally, as I shall indicate, on at least one matter of substance my opinion has been modified, namely, on the matter of acceptable risk to prospective children born following embryo transfer.

I have been asked to address the ethical issues raised by the proposed research on human in vitro fertilization, laboratory culture of and experimentation with human embryos, and the intra-uterine transfer of such embryos for the purpose of assisting human generation. In addition, I have been asked to comment on the appropriateness and wisdom of Federal funding of such research and on the implications of this work for the provision of health care.

How should one think about the ethical issues, here and in general? There are many possible ways, and it is not altogether clear which way is best. For some people, ethical issues are immediately matters of right and wrong, of purity and sin, of good and evil. For others, the critical terms are benefits and harms, risks and promises, gains and costs. Some will focus on so-called rights of individuals or groups, e.g., a right to life or childbirth; others will emphasize so-called goods for society and its members, such as the advancement of knowledge and the prevention and cure of disease. My own orientation here is somewhat different. I shall be concerned more with questions of mores, beliefs, and ethos, than with moral rules, prescriptions, and calculations. Before deciding what to do, one should try to understand the implications of doing or not doing. The first task, it seems to me, is not to ask "moral or immoral?", "right or wrong?" but to try to understand fully the meaning and significance of the proposed actions.

This concern with significance leads me to take a broad view of the matter. I urge the Board to adopt a similarly broad perspective. For we are concerned here not only with the proposed research of Dr. Soupart, and the narrow issues of safety and informed consent it immediately raises, but also with a whole range of profound matters of belief and practice, including many that are tied to definitely foreseeable consequences of this research and its predictable extensions. The very establishment of a special Ethics Advisory Board testifies that we are at least tacitly aware that more is at stake than in ordinary biomedical research or in experimenting with human subjects, at risk of bodily harm. At stake are not only possibly risk-filled conceptions of new, individual human lives, but indeed, also our very conception of the humanness of our human



life and the meaning of our embodiment, sexual being, and relation to ancestors and descendants. I urge the Board, in reaching its necessarily particular and immediate decision in the case at hand, to be mindful of the larger picture and to avoid the great danger of trivializing this matter for the sake of rendering it manageable.

I shall speak mainly about three not unrelated questions: the status and treatment of the extra-corporeal (or in vitro) embryos; questions of procreation, lineage and parenthood; and the limits of manipulation of human reproduction. Afterwards, I shall consider the question of Federal support for this research.

### The status of extra-corporeal embryos

What is the status of a fertilized human egg (=a human zygote) and the embryo that develops from it? How are we to regard its being? How are we to regard it morally, i.e., how are we to behave toward it? These are, alas, all too familiar questions. At least analogous, if not identical, questions are central to the abortion controversy and are also crucial in considering whether and what sort of experimenting is properly conducted on living aborted fetuses. Would that it were possible to say that the matter was simple and obvious, and that it had been resolved to everyone's satisfaction! But the controversy about the morality of abortion continues to rage and divide our nation. Moreover, many who favor or who do not oppose abortion do so despite the fact that they regard the pre-viable fetus as a living human organism, even if less worthy of protection than a woman's desire not to give it birth. Several witnesses before this Board have drawn attention to the centrality of this matter for your decision about laboratory culture of and experimentation with human embryos. Thus, we are obliged to take up the question of the status of the embryos, in a search for the outlines of some common ground on which many of us can stand. To the best of my knowledge, the discussion which follows is not informed by any particular sectarian or religious teaching though it may perhaps reveal that I am a person not devoid of reverence and the capacity for awe and wonder, said by some to be the core of the "religious" sentiment.

I begin by noting that the circumstances of laboratory grown blastocysts and embryos are not identical with those of the analogous cases of (1) living fetuses facing abortion and (2) living aborted fetuses used in research. First, the fetuses whose fates are at issue in abortion are unwanted, usually the result of "accidental" conception. Here, the embryos are wanted, and deliberately created, despite certain knowledge that many of them will be destroyed or discarded.<sup>4</sup> Moreover, the fate of these embryos is not in conflict with the wishes, interests, or alleged rights of the pregnant women. Second, though the DHEW guidelines governing fetal research permit studies conducted on the not-at-all viable aborted fetus,

such research merely takes advantage of available "products" of abortions undertaken not for the sake of the research. No one has proposed and no one would sanction the deliberate production of live fetuses to be aborted for the sake of research, even very beneficial research.<sup>5</sup> In contrast, we are here considering the deliberate production of embryos for the express purpose of experimentation.

The cases may also differ in other ways. Given the present state of the art, the largest embryo under discussion is the blastocyst, a spherical, relatively undifferentiated mass of cells, barely visible to the naked eye. In appearance it does not look human; indeed, only the most careful scrutiny by the most experienced scientist might distinguish it from similar blastocysts of other mammals. If the human zygote and blastocyst are more like the animal zygote and blastocyst than they are like the 12-week old human fetus (which already has a humanoid appearance, differentiated organs, and electrical activity of the brain), then there would be a much diminished ethical dilemma regarding their deliberate creation and experimental use. Needless to say, there are articulate and passionate defenders of all points of view. The fair minded thinker will confess his ignorance and consider the matter afresh.

First of all, the zygote and early embryonic stages are clearly alive. They metabolize, respire and respond to changes in the environment; they grow and divide. Second, though not yet organized into distinctive parts or organs, the blastocyst is an organic whole, self-developing, genetically unique and distinct from the egg and sperm whose union marked the beginning of its career as a distinct, unfolding being. While the egg and sperm are alive as cells, something new and alive in a different sense comes into being with fertilization. The truth of this is unaffected by the fact that fertilization takes time and is not an instantaneous event. For after fertilization is complete, there exists a new individual, with its unique genetic identity, fully potent for the self-initiated development into a mature human being, if circumstances are cooperative. Though there is some sense in which the lives of egg and sperm are continuous with the life of the new organism-to-be (or, in human terms, that the parents live on in the child or child-to-be), in the decisive sense there



is a discontinuity, a new beginning, with fertilization. After fertilization, there is continuity of subsequent development, even if the locus of the embryo alters with implantation (or birth). Any honest biologist must be impressed by these facts, and must be inclined, at least on first glance, to the view that a human life begins at fertilization. Even Dr. Robert Edwards has apparently stumbled over this truth, perhaps inadvertently, in the remark about Louise Brown attributed to him in an article by Peter Gwynne in Science Digest: "The last time I saw her, she was just eight cells in a test-tube. She was beautiful then, and she's still beautiful now!"<sup>6</sup>

But granting that a human life begins at fertilization, and comes-to-be via a continuous process thereafter, surely, one might say, the blastocyst itself is hardly a human being. I myself would agree that a blastocyst is not, in a full sense a human being--or what the current fashion calls, rather arbitrarily and without clear definition, a person. It does not look like a human being nor can it do very much of what human beings do. Yet, at the same time, I must acknowledge that the human blastocyst is (i) human in origin and (ii) potentially a mature human being, if all goes well. This too is beyond dispute; indeed it is precisely because of its peculiarly human potentialities that people propose to study it rather than the embryos of other mammals. The human blastocyst, even the human blastocyst in vitro, is not humanly nothing; it possesses a power to become what everyone will agree is a human being.

Here it may be objected that the blastocyst in vitro has today no such power, because there is now no way in vitro to bring the blastocyst to that much later fetal stage at which it might survive on its own. There are no published reports of culture of human embryos past the blastocyst stage (though this has, however, been reported in mice). The in vitro blastocyst, like the 12-week-old aborted fetus, is in this sense not viable (i.e., it is at a stage of maturation before the stage of possible independent existence). But if we distinguish, among the not-viable, between the pre-viable and the not-at-all viable, on the basis that the former though not-yet viable is capable of becoming or being made viable,<sup>7</sup> we note



a crucial difference between the blastocyst and the 12-week abortus. Unlike an aborted fetus, the blastocyst is possibly salvageable, and hence potentially viable (i.e., pre-viable), if it is transferred to a woman for implantation. It is not strictly true that the in vitro blastocyst is necessarily not-viable. Until proven otherwise, by embryo transfer and attempted implantation, we are right to consider the human blastocyst in vitro as potentially a human being and, in this respect, not fundamentally different from a blastocyst in utero. To put the matter more forcefully, the blastocyst in vitro is more "viable", in the sense of more salvageable, than aborted fetuses at most later stages, up to say 20 weeks.

This is not to say that such a blastocyst is therefore endowed with a so-called right to life, that failure to implant it is negligent homicide, or that experimental touchings of such blastocysts constitute assault and battery. (I myself tend to reject such claims, and think that the ethical questions are not best posed in terms of "rights." But I am, and I think the Board should be, impressed by the fact that many of our fellow citizens disagree; their views deserve our thoughtful consideration and respect just as much as our views deserve theirs.) But the blastocyst is not nothing; it is at least potential humanity, and as such it elicits, or ought to elicit, our feelings of awe and respect. In the blastocyst, even in the zygote, we face a mysterious and awesome power, a power governed by an immanent plan that may produce an indisputably and fully human being. It deserves our respect not because it has rights or claims or sentience (which it does not have at this stage), but because of what it is, now and prospectively.

Let us test this provisional conclusion by considering intuitively our response to two possible fates of such zygotes, blastocysts, and early embryos. First, should such an embryo die, will we be inclined to mourn its passing? When a woman we know miscarries, we are sad--largely for her loss and disappointment, but perhaps also at the premature death of a life that might have been. But we do not mourn the departed fetus, nor do we seek ritually to dispose of the remains. In this respect, we do not treat even the fetus as fully one of us.

On the other hand, we would I suppose recoil even from the thought, let

alone the practice--I apologize for forcing it upon the reader--of eating such embryos, should someone discover that they would provide a great delicacy, a "human caviar." The human blastocyst would be protected by our taboo against cannibalism which insists on the humanness of human flesh and which does not permit us to treat even the flesh of the dead as if it were mere meat. The human embryo is not mere meat; it is not just stuff; it is not a thing.<sup>8</sup> Because of its origin and because of its capacity, it commands a higher respect.

How much more respect? As much as for a fully developed human being? My own inclination is to say "probably not," but who can be certain? Indeed, there might be prudential and reasonable grounds for an affirmative answer, partly because the presumption of ignorance ought to err in the direction of not under-estimating the basis for respect (not the least for our own sake), partly because so many people feel very strongly that even the blastocyst is protectably human. As a first approximation, I would analogize the early embryo in vitro to the early embryo in utero (because both are potentially viable and human). On this ground alone, the most sensible policy is to treat the early embryo as a pre-viable fetus, with constraints imposed on early embryo research at least as great as those on fetal research.

To some this may seem excessively scrupulous. They will argue for the absence of distinctive humanoid appearance or the absence of sentience. To be sure, we would feel more restraint in invasive procedures conducted on a five month old or even a 12-week old living fetus than on a blastocyst. But this added restraint on inflicting suffering on a "look-alike," feeling creature in no way denies the propriety of a prior restraint, grounded in respect for individuated, living, potential humanity. Before I would be persuaded to treat early embryos differently from later ones, I would insist on t h e establishment of a clear, naturally-grounded boundary--I do not say a line, because no sharp line exists in the continuity which is development--which separates "early" and "late," and which provides the basis for respecting "the early" less than the "late." This burden must be accepted by proponents of experimentation with human embryos in vitro if a decision to permit creating embryos for such experimentation is to be

treated as ethically responsible.

### The treatment of extra-corporeal embryos

Where does the above analysis lead in thinking about treatment of in vitro human embryos? I indicate, very briefly, the lines toward a possible policy, though that is not my major intent.

The in vitro fertilized embryo has four possible fates: (1) implantation, in the hope of producing from it a child; (2) death, by active "killing" or disaggregation, or by a "natural" demise; (3) use in manipulative experimentation--embryological, genetic, etc.; (4) use in attempts at perpetuation in vitro, beyond the blastocyst stage, ultimately, perhaps to viability. (I will not now consider this fourth and future possibility, though I would indicate that full laboratory growth of an embryo into a viable human being (i.e. ectogenesis), while perfectly compatible with the respect owed to its potential humanity, in the present sense, may be incompatible with the respect owed to its humanity that is grounded in the bonds of lineage, the meaning of our embodiment, and the nature of parenthood).

On the strength of my analysis of the status of the embryo, and the respect due it, no objection would be raised to implantation. In vitro fertilization and embryo transfer to treat infertility, as in the case of Mr. and Mrs. Brown, is perfectly compatible with a respect and reverence for human life, including potential human life. Moreover, no disrespect is intended or practiced by the mere fact that several eggs are removed for fertilization, to increase the chance of success. Were it possible to guarantee successful fertilization and normal growth with a single egg, no more would need to be obtained. Assuming nothing further is done with the unimplanted embryos, there is nothing disrespectful going on. The demise of the unimplanted embryos would be analogous to the loss of numerous embryos wasted in the normal in vivo attempts to generate a child. It is estimated that over 50 percent of eggs successfully fertilized during unprotected sexual intercourse fail to implant, or do not remain implanted, in the uterine wall, and are shed soon thereafter, before a diagnosis of



pregnancy could be made. Any couple attempting to conceive a child tacitly accepts such unintended and unavoidable embryonic wastage as the perfectly acceptable price to be paid for the birth of a (usually) healthy child. Current procedures to initiate pregnancy with laboratory fertilization thus differ from the natural "procedure" in that what would normally be spread over four or five months in vivo is compressed into a single effort, using all at once a four or five months' supply of eggs.<sup>9</sup>

Parenthetically, we should note that the natural occurrence of embryo and fetal loss and wastage does not necessarily or automatically justify all deliberate, humanly caused destruction of fetal life. For example, the natural loss of embryos in early pregnancy cannot in itself be a warrant for deliberately aborting them or for invasively experimenting on them in vitro, any more than stillbirths could be a justification for newborn infanticide. There are many things that happen naturally that we ought not to do deliberately. It is curious how the same people who deny the relevance of nature as a guide for evaluating human interventions into human generation, and who deny that the term "unnatural" carries any ethical weight, will themselves appeal to "nature's way" when it suits their purposes.<sup>10</sup> Still, in this present matter, the closeness to natural procreation--the goal is the same, the embryonic loss is unavoidable and not desired, and the amount of loss is similar--leads me to believe that we do no more intentional or unjustified harm in the one case than in the other, and practice no disrespect.

But must we allow these unimplanted embryos to die? Why should they not be either transferred for "adoption" into another infertile woman, or else used for investigative purposes, to seek new knowledge, say about gene action? The first option raises questions about the nature of parenthood and lineage to which I will return. But on first glance, it would seem to raise large questions, especially when the original couple was seeking a child of their own, and not the dissemination of their "own" biological children for pre-natal adoption.

But what about experimentation on such blastocysts and early embryos? Is that compatible with the respect they deserve? This is the hard question. On balance, I would think not. Invasive and manipulative experi-



ments involving such embryos very likely presume that they are things or mere stuff, and deny the fact of their possible viability. Certain observational and non-invasive experiments might be different. But on the whole, I would think that the respect for human embryos for which I have argued--I repeat, not their so-called right to life--would lead one to oppose most potentially interesting and useful experimentation. This is a dilemma, but one which cannot be ducked or defined away. Either we accept certain great restrictions on the permissible uses of human embryos or we deliberately decide to override--but I hope not deny--the respect due the embryos.

I am aware that I have pointed toward a seemingly paradoxical conclusion about the treatment of the unimplanted embryos: leave them alone, and do not create embryos for experimentation only. To let them die "naturally" would be the most respectful course, grounded on a respect, generically, for their potential humanity, and, individually, for their being the seed and offspring of a particular couple, who were themselves seeking only to have a child of their own. An analysis which stressed a "right to life," rather than respect, would of course lead to different conclusions. Only an analysis of the status of the embryo which denied both its so-called rights or its worthiness of all respect would have no trouble sanctioning its use in investigative research, donation to other couples, commercial transactions, and so forth.

### Risks to prospective children

The attempt to generate a child with the aid of in vitro fertilization constitutes an experiment upon the prospective child. It thus raises a most peculiar question for the ethics of human experimentation: can one ethically choose for a yet hypothetical, unconceived child-to-be, the unknown hazards he must face, obviously without his consent, and simultaneously choose to give him life in which to face them? This question has been much debated, as it points to a serious and immediate ethical concern: the hazards of manipulating the embryo as it bears on the health of the child-to-be.

Everyone agrees that human embryo transfer for the sake of generation

should not be performed until prior laboratory research in animals has provided a sound basis for estimating the likely risks to any human beings who will be born as result of this transfer and gestation. Argument centers on whether a sufficiently sound basis for estimating the likely risks to humans can be provided by animal experiments, and, if so, whether adequate experimentation has been done, and on what level risk is acceptable.

There is, it still seems to me, good reason for insisting that risk of incidence and likely extent of possible harm be very, very low, lower, say, than in therapeutic experimentation in children or adults. But I do not think that the risk of harm must be positively excluded (and it certainly cannot be). It would suffice if those risks were equivalent to or less than the risks to the child from normal procreation. To insist on more rigorous standards, especially when we permit known carriers of genetic disease to reproduce, would seem a denial of equal treatment to infertile couples contemplating in vitro assistance. Moreover, it is to give undue weight to the importance of bodily harm over against the risks of poor nurture and rearing after birth. Wouldn't the couple's great eagerness for the child count, in the promise of increased parental affection, toward offsetting even a slightly higher but unknown risk of mental retardation? Finally, to insist on extra-scrupulosity regarding risks in laboratory-assisted reproduction is to attach too much of one's concern about such laboratory reproduction to the wrong issues. True, everyone understands about harming children, while very few worry about dehumanization of procreation or problems of lineage. But those are the things that are distinctive about laboratory-assisted reproduction, and not the risk of bodily harm to offspring. It should suffice that the risks be comparable to those for ordinary procreation, not greater but no less.

It remains a question whether we now know enough about these risks to go ahead with human embryo transfer. Here I would defer to the opinions of the cautious experts--for caution is the posture of responsibility toward such prospective children. I would agree with Doctors Luigi Mastroianni, Benjamin Brackett, and Robert Short that the risks

for humans has not yet been sufficiently assessed, in large part because the risks in animals have been so poorly assessed (due to the small numbers of such births and to the absence of any prospective study to identify and evaluate deviations from the norm).

### Questions of Procreation, Lineage, and Parenthood

Many people rejoiced at the birth of Louise Brown. Some were pleased by the technical accomplishment, many were pleased that she was born apparently in good health. But most of us shared the joy of her parents, who after a long, frustrating and fruitless period, at last had the pleasure and blessing of a child of their own. The desire to have a child of one's own is acknowledged to be a powerful and deep-seated human desire--some have called it "instinctive"--and the satisfaction of this desire, by the relief of infertility, is said to be one major goal of continuing work with in vitro fertilization and embryo transfer. That this is a worthy goal few, if any, would deny--even those who fear or deplore the artificial means here employed, or who would prefer to support research on prevention rather than cure, would wish to see such involuntary infertility relieved and to see each married couple able, if willing, to experience the joys and the solemn responsibilities of parenthood.

Yet let us explore what is meant by "to have a child of one's own." First, what is meant by "to have"? Is the crucial meaning that of gestating and bearing? Or is it "to have" as a possession? Or is it to nourish and to rear, the child being the embodiment of one's activity as teacher and guide? Or is it rather to provide someone who descends and comes after, who will replace one in the family line or preserve the family tree by new sproutings and branchings?

More significantly, what is meant by "one's own"? What sense of one's own is important? A scientist might define "one's own" in terms of carrying one's own genes. Though in some sense correct, this cannot be humanly decisive. For Mr. Brown or for most of us, it would not be a matter of indifference if the sperm used to fertilize the egg were provided by our identical twin brother, whose genes were, of course, the same as ours. Rather, the humanly crucial sense of "one's own," the sense that



leads most people to choose their own, rather than to adopt, is captured in such phrases as "my seed," "flesh of my flesh," "sprung from my loins." More accurately, since one's own is not the own of one but of two, the desire to have a child of one's own is a couple's desire to embody, out of the conjugal union of their separate bodies, a child who is flesh of their separate flesh made one. This archaic language may sound quaint and may seem to the enlightened mind but a vestige of a primitive stage of human self-understanding. But I would argue that this is precisely what is being celebrated by most people who rejoice at the birth of Louise Brown, whether they would articulate it this way or not. Mr. and Mrs. Brown here fulfill this aspect of their separate sexual natures and of their married life together, they acquire descendants and a new branch on their joined family tree, and the child Louise is given solid and unambiguous roots from which she has sprung and by which she will be nourished.

If this were to be the only use made of embryo transfer, and if providing in this sense "a child of one's own" were indeed the sole reason for the clinical use of the techniques, there could be no objection on this score. Here indeed is an affirmation of transmission and the importance of lineage and connectedness. Yet there will almost certainly be other uses, involving third parties, (fourth parties, if one remembers the fertilizing role of the scientist), to satisfy the desire "to have" a child of "one's own" in different senses of "to have" and "one's own." I am not merely speculating about future possibilities. With the technology to effect human in vitro fertilization and embryo transfer comes the immediate possibility of egg donation (egg from donor, sperm from husband), embryo donation (egg and sperm from outside of the marriage), and foster pregnancy (host surrogate for gestation). Nearly everyone agrees that these circumstances are morally and perhaps psychologically more complicated than the intra-marital case. Here the meaning of "one's own" is no longer so unambiguous; neither is the meaning of motherhood and the status of pregnancy. On the one hand, it is argued that embryo donation, or "prenatal adoption," would be superior to present adoption, because the woman would have the experience of pregnancy and the child



would be born of the "adopting" mother, rendering the maternal tie even more close. On the other hand, the mother-child bond rooted in pregnancy and delivery is held to be of little consequence by those who would endorse the use of surrogate gestational "mothers," say for a woman whose infertility is due to uterine disease rather than ovarian disease or oviduct obstruction. Clearly, the "need" and demand for extra-marital embryo transfer are real and probably large, probably even greater than the intra-marital ones. Already, the Chairman of the Ethics Advisory Board has testified in Congress about the need to define the responsibilities of the donor and the recipient "parents." Thus the new techniques will not only serve to ensure and preserve lineage, but will also serve to confound and complicate it. The principle truly at work here is not to provide married couples with a child of their own, but to provide anyone who wants one with a child, by whatever possible or convenient means.

"So what?" it will be said. First of all, we already practice and encourage adoption. Second, we have permitted artificial insemination donor--though we have, after some forty years of this practice, yet to resolve questions of legitimacy. Third, what with the high rate of divorce and remarriage, identification of "mother," "father," and "child" are already complicated. Fourth, there is a growing rate of illegitimacy and husbandless parentages. Fifth, the use of surrogate mothers for foster pregnancy has already occurred, with the aid of artificial insemination.<sup>11</sup> Finally, our age in its enlightenment is no longer so certain about the virtues of family, lineage, and heterosexuality, or even about the taboos against adultery and even incest. Against this background, it will be asked, why all the fuss about some little embryos that stray from the nest?

It is not an easy question to answer. Yet consider. We practice adoption because there are abandoned children who need a good home. We do not, and would not, encourage people deliberately to generate children for others; partly we wish to avoid baby markets, partly we think it unfair to the child deliberately to deprive him of his natural ties. Recent years have seen a rise in our concern with roots, against the rootless and increasingly homogeneous background of contemporary American life. Adopted children, in particular, are pressing for information regarding

their "real parents," and some states now require that such information be made available (on that typically modern ground of "freedom of information," rather than because of the profound importance of lineage for self-identity). The practice of artificial insemination donor has yet to be evaluated, the secrecy in which it is practiced being an apparent concession to the dangers of publicity.<sup>12</sup> Indeed, most physicians who practice artificial insemination donor routinely mix in some semen from the husband, to preserve some doubt about paternity--again, a concession to the importance of lineage and legitimacy. Finally, what about the changing mores of marriage, divorce, single-parent families, and sexual behavior? Do we applaud these changes? Do we want to contribute further to the confusion of thought, identity, and practice?<sup>13</sup>

Properly understood, the largely universal taboos against incest, and also the prohibition against adultery, suggest that clarity about who your parents are, clarity in the lines of generation, clarity about who is whose, are the indispensable foundations of a sound family life, itself the sound foundation of civilized community. Clarity about your origins is crucial for self-identity, itself important for self-respect. It would be, in my view, deplorable public policy further to erode such fundamental beliefs, values, institutions, and practices. This means, concretely, no encouragement of embryo adoption or especially of surrogate pregnancy. While it would be perhaps foolish to try to proscribe or outlaw such practices, it would not be wise for the Federal government to foster them. The Ethics Advisory Board should carefully consider whether it should and can attempt to restrict the use of embryo transfer to the married couple from whom the embryo derives.

The case of surrogate wombs bears a further comment. While expressing no objection to the practice of foster pregnancy itself, some people object that it will be done for pay, largely because of their fear that poor women will be exploited by such a practice. But if there were nothing wrong with the practice, what would be wrong with making a living at it? Clearly this objection harbors a tacit understanding that to bear another's child is in some sense a degradation of oneself. It is to deny the meaning and worth of one's body, to treat it as a mere incubator, divested of its

human meaning. The buying and selling of human flesh and the dehumanized uses of the human body ought not to be encouraged. To be sure, the practice of womb donation could be engaged in for love not money, as it apparently has been in the case in Michigan. A woman could bear her sister's child. But to the degree that one escapes in this way from the degradation and difficulties of the sale of human flesh and bodily services and the treating of the body as stuff (the problem of cannibalism), one approaches instead the difficulties of incest and near incest.

### Limits on Manipulation of Human Reproduction

Objections have been raised about the deliberate technological intervention into the so-called natural processes of human reproduction. Some would simply oppose such interventions as "unnatural," and therefore wrong. Others are concerned about the consequences of these interventions, and about their ends and limits. Again, I think it important to explore the meaning and possible significance of such interventions, present and projected, especially as they bear on fundamental beliefs, institutions, and practices. To do so requires that we consider likely future developments in the laboratory study of human reproduction. Indeed, I shall argue that the Board must consider such future developments in reaching its decision in the present case.

What can we expect in the way of new modes of reproduction, as an outgrowth of present studies? To be sure, prediction is difficult. One can never know with certainty what will happen, and all the more so, how soon. But this difficulty also affects the predictions made, in support of the research, regarding likely advances in basic knowledge about human development and in new techniques for contraception, abortion, gene therapy, etc. To be seriously and fairly agnostic, we must admit uncertainty about all aspects of the future.

Yet uncertainty is not the same as simple ignorance. Some things, indeed, seem likely. They seem likely because (1) they are thought necessary or desirable, at least by some researchers and their sponsors, (2) they are probably biologically possible and technically feasible, and (3) they will be difficult to prevent or control (especially if no one anti-



cipates their development or sees a need to worry about them). One of the things the citizenry, myself included, would expect from an Ethics Advisory Board and our policy makers generally is that they face up to reasonable projections of future accomplishments, consider whether they are cause for social concern, and see whether or not the principles now enunciated and the practices now established are adequate to deal with any such concerns.

I project at least the following:

1. The growth of human embryos in the laboratory will be extended beyond the blastocyst stage. Such growth must be deemed desirable under all arguments advanced for developmental research up to the blastocyst stage; research on gene action, chromosome segregation, cellular and organic differentiation, fetus-environment interaction, implantation, etc., cannot answer all its questions with the blastocyst. Such in vitro post-blastocyst differentiation has apparently been achieved in the mouse, in culture; the use of other mammals as temporary hosts for human embryos is also a possibility. How far such embryos will eventually be perpetuated is anybody's guess, but full-term ectogenesis cannot be excluded. Neither can the existence of laboratories filled with many living human embryos, growing at various stages of development.

2. Experiments will be undertaken to alter the cellular and genetic composition of these embryos, at first without subsequent transfer to a woman for gestation, perhaps later as a prelude to reproductive efforts. Again, scientific reasons now justifying Dr. Soupart's research already justify further embryonic manipulations, including formations of hybrids or chimeras (intra-specific and inter-specific); gene, chromosome, and plasmid insertion, excision, or alteration; nuclear transplantation or cloning, etc. The techniques of DNA recombination, coupled with the new skills of handling embryos, make prospects for some precise genetic manipulation much nearer than anyone would have guessed ten years ago. And embryological and cellular research in mammals is making astounding progress. On the cover of a recent issue of Science is the picture of a hexaparental mouse, born after reaggregation of an early embryo with cells disaggregated from three separate embryos (Note: This sober journal calls



this a "Handmade mouse"--i.e. literally a manu-factured mouse--and goes on to say that it was "manufactured by genetic engineering techniques."<sup>14</sup>

3. Storage and banking of living human embryos (and ova) will be undertaken, perhaps commercially. Commercial sperm banks are already well established and prospering.

Space does not permit me to do more than identify a few kinds of questions that must be considered in relation to the possible coming control over human heredity and reproduction: questions about the wisdom required to engage in such practices; questions about the goals and standards that will guide our interventions (e.g., In the absence of ends and standards for the use of our rationalized technique, are we truly in control, or are we really, perhaps more than ever, at the mercy of chance?); questions about changes in the concepts of being human, including embodiment, gender, love, lineage, identity, parenthood, and sexuality; questions about the responsibility of power over future generations; questions about awe, respect, humility; questions about the kind of society we will have if we follow along our present course. Some of these questions are addressed, albeit too briefly and polemically, in the latter part of my "Making Babies" article, to which I would refer you.

Though I cannot discuss these questions now, I can and must face a serious objection to considering them at all. Most people would agree that the projected possibilities raise far more serious questions than do simple fertilization of a few embryos, their growth in vitro to the blastocyst stage, and their possible transfer to women for gestation. Why burden the present decision with these possibilities? Future "abuses," it is often said, do not disqualify present uses (though, these same people also often say that "future benefits justify present questionable uses.") Moreover, there can be no certainty that A will lead to B. This thin-edge-of-the-wedge argument has been open to criticism.

But such criticism misses the point, for two reasons. First, critics often misunderstand the wedge argument. The wedge argument is not primarily an argument of prediction, that A will lead to B, say on the strength of the empirical analysis of precedent and an appraisal of the likely direction of present research. It is primarily an argument about the logic of

justification. Do the principles of justification now used to justify the current research proposal already justify in advance the further developments? Consider some of these principles.

1. It is desirable to learn as much as possible about the processes of fertilization, growth, implantation, and differentiation of human embryos and about human gene expression and its control.

2. It would be desirable to acquire improved techniques for enhancing conception and implantation, for preventing conception and implantation, for the treatment of genetic and chromosomal abnormalities, etc.

3. Finally, only research using human embryos can answer these questions and provide these techniques.

4. There should be no censorship or limitation of scientific inquiry or research.

This logic knows no boundary at the blastocyst stage, or for that matter, at any later stage. For these principles not to justify future extensions of current work, some independent additional principles limiting such justification to particular stages of development would have to be found. Here your task is to find such a biologically defensible distinction that could be respected as reasonable and not arbitrary, a difficult--perhaps impossible-- task, given the continuity of development after fertilization. The citizenry, myself included, will want to know precisely what grounds you will have for endorsing Soupart's research, and whether your principles have not already sanctioned future developments. If you do give such wedge-opening justifications, please do so deliberately, candidly, and intentionally.

A better case to illustrate the wedge logic is the principle offered for the embryo transfer procedures, as treatment for infertility. Will you support the use of in vitro fertilization and embryo transfer because it provides a "child of one's own," in a strict sense of one's own, to a married couple? Or will you support the transfer because it is treatment of involuntary infertility, which deserves treatment in or out of marriage, hence endorsing the use of any available technical means (that would produce a healthy and normal child), including surrogate wombs, or even ecto-

genesis?

Second, logic aside, the opponents of the wedge argument do not counsel well. It would be simply foolish to ignore what might come next, and to fail to make the best possible assessment of the implications of present action (or inaction). Let me put the matter very bluntly: this Board, in the decision it must now make, may very well be helping to decide whether human beings will eventually be produced in laboratories. I say this not to shock--and I do not mean to beg the question of whether that would be desirable or not. I say this to make sure that you face squarely the full import and magnitude of your decision. Once the genies let the babies into the bottle, it may be impossible to get them out again.

#### Federal Funding: THE Policy Question

So much, then, for the meaning of initiating and manipulating human embryos in the laboratory. These considerations still make me doubt the wisdom of proceeding with these practices, both in research and in their clinical application, notwithstanding that valuable knowledge might be had by continuing the research and identifiable suffering might be alleviated by using it to circumvent infertility. To doubt the wisdom of going ahead makes one at least a fellow-traveller of the opponents of such research, but it does not, either logically or practically, require that one join them in trying to prevent it, say by legal prohibition. Not every folly can or should be legislated against. Attempts at prohibition here would seem to be both ineffective and dangerous, ineffective because impossible to enforce, dangerous because the costs of such precedent-setting interference with scientific research might be greater than the harm it prevents. To be sure, we already have legal restrictions on experimentation with human subjects, which restrictions are manifestly not incompatible with the progress of medical science. Neither is it true that science cannot survive if it must take some direction from the law. Nor is it the case that all research, because it is research, is or should be absolutely protected. But it does not seem to me that in vitro fertilization and embryo transfer deserve, at least at



present, to be treated as sufficiently dangerous for legislative interference.

But if to doubt the wisdom does not oblige one to outlaw the folly, neither does a decision to permit require a decision to encourage or support. A researcher's freedom to do in vitro fertilization, or a woman's right to have a child with laboratory assistance, in no way implies a public (or even a private) obligation to pay for such research or treatment. A right against interference is not an entitlement for assistance. The question before the Ethics Advisory Board and the Department of Health, Education, and Welfare is not whether to permit such research but whether the Federal government should fund it. This is the policy question that needs to be discussed.

The arguments in favor of Federal support are well known. First, the research is seen as continuous with, if not quite an ordinary instance of, the biomedical research which the Federal government supports handsomely; roughly two-thirds of the money spent on biomedical research in the United States comes from Uncle Sam. Why is this research different from all other research? Its scientific merit has been attested to by the normal peer review process at NIH. For some, that is a sufficient reason to support it.

Second, there are specific practical fruits anticipated from the anticipated successes of this new line of research. Besides relief for many cases of infertility, the research promises new birth-control measures based upon improved understanding of the mechanisms of fertilization and implantation, which in turn could lead to techniques for blocking these processes. Also, studies on early embryonic development hold forth the promise of learning how to prevent some congenital malformations and certain highly malignant tumors (e.g., hydatidiform mole) that derive from aberrant fetal tissue.

Third, as he who pays the piper calls the tune, Federal support would make easy the Federal regulation and supervision of this research. For the government to abstain, so the argument runs, is to leave the control of research and clinical application in the hands of profit hungry, adventurous, insensitive, reckless, or power hungry private physicians, scientists,



or drug companies, or, on the other hand, at the mercy of the vindictive, mindless, and superstitious civic groups that will interfere with this research through state and local legislation. Only through Federal regulation, which, it is said, can only follow with Federal funding, can we have reasonable, enforceable, and uniform guidelines.

Fourth is the chauvinistic argument that the United States should lead the way in this brave new research, especially as it will apparently be going forward in other nations. Indeed, one witness testifying before the Ethics Advisory Board deplored the fact that the first Louise Brown was British and not American, and complained, in effect, that the existing moratorium on Federal support has already created what one might call an "in vitro fertilization gap." The pre-eminence of American science and technology, so the argument implies, is the center of our pre-eminence among the nations, a position which will be jeopardized if we hang back out of fear.

Let me respond to these arguments, in reverse order. Conceding the premise of the importance of American science for American prestige and strength, it is far from clear that failure to support this research would jeopardize American science. Certainly the use of embryo transfer to overcome infertility, though a vital matter for the couples involved, is hardly a matter of vital national interest--at least not unless and until the majority of American women are similarly infertile. The demands of international competition, admittedly often a necessary evil, should be invoked only for things that really matter; a missile gap and an embryo transfer gap are chasms apart. In areas not crucial to our own survival, there will be many things we should allow other nations to develop, if that is their wish, without feeling obliged to join them. Moreover, one should not rush into potential folly to avoid being the last to commit it. If this new research were to prove to be the first and irrevocable step toward Brave New World, would we regret that it was someone else who took it?

The argument about governmental regulations has much to recommend it. But it fails to consider that there are other safeguards against recklessness, at least in the clinical applications, known to the high-minded as the canons of medical ethics and to the cynical as liability for malpractice.

Also, Federal regulations attached to Federal funding will not regulate research done with private monies, say by the drug companies. Moreover, there are enough concerned practitioners of these new arts who would have a compelling interest in regulating their own practice, if only to escape the wrath and interference of hostile citizen groups in response to unsavory goings-on. The available evidence does not convince me that a sensible practice requires regulation by the Federal government.

In turning to the argument about anticipated technological powers, we face difficult calculations, of unpredictable and more-or-less likely costs and benefits, and the all-important questions of priorities in the allocation of scarce resources. Here it seems useful to consider separately the techniques for generating children and the anticipated techniques for birth control or for preventing developmental anomalies and malignancies.

First, accepting that providing a child of their own to infertile couples is a worthy goal--and it is both insensitive and illogical to cite the population problem as an argument for ignoring the problem of infertility--one can nevertheless question its rank relative to other goals of medical research. One can even wonder--and I have done so in print--whether it is indeed a medical goal, or a worthy goal for medicine, that is, whether alleviating infertility, especially in this way, is part of the art of healing.<sup>15</sup> Just as abortion for genetic defect is a peculiar innovation in medicine (or in preventive medicine) in which a disease is treated by eliminating the patient (or, if you prefer, a disease is prevented by 'preventing' the patient), so laboratory-fertilization is a peculiar treatment for oviduct obstruction, in that it requires the creation of a new life to "heal" an existing one. All this simply emphasizes the uniqueness of the reproductive organs, in that their proper function involves other people, and calls attention to the fact that infertility is not a "disease" like heart disease or stroke, even though obstruction of a normally patent tube or vessel is the proximate cause of each.

However this may be--one must surely grant that treatment of infertility is at best on the periphery of medicine, and that childlessness is more than a bodily defect--there is a more important objection to this approach to the problem. It represents yet another instance of our thoughtless preference for expensive, high-technology, therapy-oriented approaches

to disease and dysfunctions. What about spending this money on discovering the causes of infertility? What about the prevention of tubal obstruction? We complain about rising medical costs, but we insist on the most spectacular and the most technological--and thereby the most costly--remedies.

The truth is that we know a little about the causes of tubal obstruction--though much less than we should or could. For instance, it is estimated that at least one-third of such cases are the aftermath of pelvic-inflammatory disease, caused by that uninvited venereal guest, gonococcus. Leaving aside any question about whether it makes sense for a federally funded baby to be the wage of aphrodisiac indiscretion, one can only look with wonder at a society that will have "petri-dish babies"<sup>16</sup> before it has found a vaccine against gonorrhea.

True, there are other causes of blocked oviducts, and blocked oviducts are not the only cause of female infertility. True, it is not logically necessary to choose between prevention and cure. But practically speaking, with money for research as limited as it is, research funds targeted for the relief of infertility should certainly go first to epidemiological and preventive measures--especially where the costs of success in the high-technology cure are likely to be great.

What about these costs? I have already explored some of the non-financial costs, in discussing the meaning of this research for our images of humanness. Let us, for now, consider only the financial costs. How expensive was Louise Brown? We do not know, partly because Drs. Edwards and Steptoe have yet to publish their results, indicating how many failures preceded their success, how many procedures for egg removal and for fetal monitoring were performed on Mrs. Brown, and so on. One must add in the costs of monitoring the baby's development to check her "normality"--we must also remember the psychic cost to Louise, a matter her media-happy doctors and society have chosen to ignore--and, should, it come, the costs of governmental regulation. A conservative estimate might place the costs of a successful pregnancy to be between five and ten thousand dollars. If we use the conservative figure of 500,000 for estimating the number of infertile women with blocked oviducts in the United States whose only hope



of having children lies in in vitro fertilization,<sup>17</sup> we reach a conservative estimated cost of 2.5 to 5 billion dollars. Should technical improvement someday lower the costs to \$1,000 per baby, the estimated cost would still be half-a-billion dollars. Is it really even fiscally wise for the Federal government to start down this road?

Clearly not, if it is also understood that the costs of providing the service, based on a successful technology, will also be borne by the taxpayers. Nearly everyone now agrees that the kidney machine legislation, obliging the Federal government to pay about \$25,000-\$30,000 per patient per year for kidney dialysis for anyone in need (cost to the taxpayers for 1978 is nearly \$ 1 billion), is an impossible precedent, if not an outright mistake --notwithstanding that individual lives have been prolonged as a result. But once the technique of in vitro fertilization and embryo transfer is developed and available, how should the baby-making be paid for? Should it be covered under medical insurance? If a National Health Insurance program is enacted, will and should these services be included? (Those who argue that they are part of medicine will have a hard time saying no.) Failure to do so will make this procedure available only to the well-to-do, on a fee-for-service basis. Would that be a fair alternative? Perhaps; but it is unlikely to be tolerated. Indeed, the principle of equality--equal access to equal levels of medical care--is the leading principle in the press for medical reform. One can be certain that efforts will be forthcoming to make this procedure available equally to all, independent of ability to pay, under Medicaid or National Health Insurance or in some other way. (I have recently learned that a Boston-based group concerned with infertility has obtained private funding to pay for artificial insemination for women on welfare!!)

Much as I sympathize with the plight of infertile couples, I do not believe that they are entitled to the provision of a child at the public expense, especially now, especially at this cost, especially by a procedure that also involves so many moral difficulties. Given the many vexing dilemmas that will surely be spawned by laboratory-assisted reproduction, the Federal government should not be misled by compassion to embark on this imprudent course.



To consider briefly the Federal funding of the research for its other anticipated technological benefits, independent of its clinical use in baby-making, we face here a more difficult matter. As is the case with all basic research, one simply cannot predict what kinds of techniques it will yield. But here, also, I think good sense would at present say no. Before one undertakes human in vitro fertilization to seek new methods of birth control--e.g., by developing antibodies to the human egg that would physically interfere with its fertilization--one should make adequate attempts to do this in animals. One simply can't get large enough numbers of human eggs to do this pioneering research well--at least not without subjecting countless women to additional risks not for their immediate benefit. Why not test this conceit first in the mouse or rabbit? Only if the results were very promising--and judged also to be relatively safe in practice--should one consider trying such things in humans. Likewise, the developmental research can and should be first carried out in animals, especially in primates. Though in vitro fertilization has yet to be achieved in monkeys, embryo transfer of in vivo fertilized eggs has been accomplished, thus permitting the relevant research to proceed. Purely on scientific grounds, the Federal government ought not now to be investing its funds in this research for its promised technological benefits, benefits which, in the absence of pilot studies in animals, must be regarded as mere wishful thoughts in the imaginings of scientists.

There remains the first justification, research for the sake of knowledge: knowledge about cell cleavage, cell-cell and cell-environment interactions, and cell differentiation; knowledge of gene action and its regulation; knowledge of the effects and mechanisms of action of various chemical and physical agents on growth and development; knowledge of the basic processes of fertilization and implantation. This is all knowledge worth having, and though much can be learned using animal sources--and these sources have barely begun to be sufficiently exploited--the investigation of these matters in man would, sooner or later, require the use of human embryonic material. Here, again, there are questions of research priority about which there is room for disagreement, among scientists and laymen

alike. But these questions of research priority, while not irrelevant to the decision at hand, are not the questions that the Ethics Advisory Board was constituted to answer.

It was constituted to consider whether such research is consistent with the ethical standards of our community. The question turns in part on the status of the early embryo. If, as I have argued, the early embryo is deserving of respect because of what it is, now and potentially, it is difficult to justify submitting it to invasive experiments, and especially difficult to justify creating it solely for the purpose of experimentation. But even if this argument fails to sway the Board, another one should. For your decision, I remind you, is not whether in vitro fertilization should be permitted in the United States, but whether our tax dollars should encourage and foster it. One cannot, therefore, ignore the deeply held convictions of a sizeable portion of our population --it may even be a majority on this issue-- that regards the human embryo as protectable humanity, not to be experimented upon except for its own benefit. Never mind if these beliefs have a religious foundation--as if that should ever be a reason for dismissing them. The presence, sincerity, and depth of these beliefs, and the grave importance of their subject, is what must concern us. The holders of these beliefs have been very much alienated by the numerous court decisions and legislative enactments regarding abortion and research on fetuses. Many who by-and-large share their opinions about the humanity of pre-natal life have with heavy heart gone along with the liberalization of abortion, out of deference to the wishes, desires, interests or putative rights of pregnant women. But will they go along here with what they can only regard as gratuitous and willful assaults on human life, or at least on potential and salvageable human life, and on human dignity? We can ill afford to alienate them further, and it would be unstatesmanlike, to say the least, to do so, especially in a matter so little important to the national health and one so full of potential dangers.

Technological progress can be but one measure of our national health. Far more important is the affection and esteem in which our citizenry holds its laws and institutions. No amount of relieved infertility is

worth the further disaffection and civil contention that the lifting of the moratorium on Federal funding is likely to produce. People opposed to abortion and people grudgingly willing to permit women to obtain elective abortion, at their own expense, will not tolerate having their tax money spent on scientific research requiring what they regard as at best, cruelty, at worst, murder. A prudent Ethics Advisory Board and a prudent and wise Secretary of Health, Education, and Welfare should take this matter most seriously, and refuse to lift the moratorium--at least until they are persuaded that public opinion will overwhelmingly support them. Imprudence in this matter may be the worst sin of all.

### An Afterword

This has been for me a long and difficult exposition. Many of the arguments are hard to make. It is hard to get confident people to face unpleasant and future prospects. It is hard to get people to take seriously such "soft" matters as lineage, identity, respect, and self-respect when they are in tension with such "hard" matters as a cure for infertility or new methods of contraception. It is hard to talk about the meaning of sexuality and embodiment in a culture that treats sex increasingly as sport and that has trivialized the significance of gender, marriage, and procreation. It is hard to oppose Federal funding of baby-making in a society which increasingly demands that the Federal government supply all demands, and which--contrary to so much evidence of waste, incompetence, and corruption--continues to believe that only Uncle Sam can do it. And, finally, it is hard to speak about restraint in a culture that seems to venerate very little above man's own attempt to master all. Here, I am afraid, is the biggest question and the one we perhaps can no longer ask or deal with: the question about the reasonableness of the desire to become masters and possessors of nature, human nature included.

Here we approach the deepest meaning of in vitro fertilization. Those who have likened it to artificial insemination are only partly correct. With in vitro fertilization, the human embryo emerges for the first time from the natural darkness and privacy of its own mother's womb where it is hidden away in mystery, into the bright light and utter publicity of



the scientist's laboratory, where it will be treated with unswerving rationality, before the clever and shameless eye of the mind and beneath the obedient and equally clever touch of the hand. What does it mean to hold the beginning of human life before your eyes, in your hands--even for 5 days, for the meaning does not depend on duration? Perhaps the meaning is contained in the following story.

Long ago there was a man of great intellect and great courage. He was a remarkable man, a giant, able to answer questions that no other human beings could answer, willing boldly to face any challenge or problem. He was a confident man, a masterful man. He saved his city from disaster and ruled it as a father rules his children, revered by all. But something was wrong in his city. A plague had fallen on generation; infertility afflicted plants, animals and human beings. The man confidently promised to uncover the cause of the plague and to cure the infertility. Resolutely, confidently, he put his sharp mind to work to solve the problem, to bring the dark things to light. No secrets, no reticences, a full public inquiry. He raged against the representatives of caution, moderation, prudence, and piety, who urged him to curtail his inquiry; he accused them of trying to usurp his rightfully earned power, to replace human and masterful control with submissive reverence. The story ends in tragedy: he solved the problem but, in making visible and public the dark and intimate details of his origins, he ruined his life, and that of his family. In the end, too late, he learns about the price of presumption, of overconfidence, of the overweening desire to master and control one's fate. In symbolic rejection of his desire to look into everything, he punishes his eyes with self-inflicted blindness. Sophocles seems to suggest that such a man is always in principle--albeit unwittingly--a patricide, a regicide, and a practitioner of incest. We men of modern science may have something to learn from our forebearer Oedipus. It appears that Oedipus, being the kind of man an Oedipus is (the chorus calls him a paradigm of man), had no choice but to learn through suffering. Is it really true that we too have no other choice?



## Recommendations to the Ethics Advisory Board

My recommendations are of two sorts, formal and substantive. The former concern the kinds of things your recommendations or guidelines should contain, the latter address the content of your decisions or recommendations.

### I. Formal

- A. You should include a clear statement about the status of living human zygotes and early embryos, and what such status might imply for how they are to be treated. The statement should set forth relevant differences between the human embryos and (1) non-human embryos, (2) human gametes, (3) human organs and tissues, and should acknowledge that the embryos are pre-viable or potentially viable.
- B. If you fund this research, state clearly and precisely the principles justifying your decision, taking into account possible future uses and extensions of this work. The principles should provide some guidance concerning: (1) acceptable limits on possible further growth of embryos in vitro beyond the blastocyst stage; (2) acceptable manipulations, if any, and unacceptable manipulations, if any, to be performed on the embryos; (3) acceptable hosts for the receipt of any embryos transferred.
- C. If you do not fund this research, state clearly and precisely the principles justifying your decision, and indicate what kinds of things might lead you to change your mind.
- D. If you permit manipulation, invasive, harmful or destructive research on the early embryos, you should try to distinguish and establish--if you can--the stage of development before which such research is acceptable and after which it is not, such that researchers and the public may know how much farther we may, at present, be allowed to go. Failure to do this can only be construed as your endorsement of the absence of any such limits.

### II. Substantive

#### A. First choice

No Federal funding for Dr. Soupart's research or any other research on human in vitro fertilization, embryo culture, and embryo transfer. The reasons include all of the following:

- (1) Much of this research is not compatible with the respect due the human embryo;
- (2) Federal support is imprudent in the face of strong public

sentiment that regards such research as immoral;

- (3) It will be difficult to forestall dangerous present and future applications of this research and its logical extensions, a powerful argument in this case because the stakes in basic values, beliefs and mores are so high;
- (4) This research continues our unwise preference for expensive, high-technology, cure-oriented approaches to public health problems, and, in its clinical application, is likely to be an enormous financial burden on an already over-burdened Federal health budget;
- (5) This research is not in any sense imperative; indeed, it would seem to be of rather low priority for Federal health research expenditure.

B. Second choice

Should the Board find the totally negative judgement unacceptable, I offer the following two-part alternative:

1. No Federal support of human in vitro fertilization for clinical use, UNTIL
  - a. Further (and prospective) animal studies give more reassurance that the offspring-to-be will be at no increased risk of harm;
  - b. Further evidence is available regarding practice and successes abroad, and their costs;
  - c. Clear guidelines are established regarding extra-marital uses of embryo transfer.
2. No Federal support of human in vitro fertilization for research purposes, at least UNTIL:
  - a. There is clear evidence that there are especially important and significant questions for which animal experimentation is impossible.
  - b. Clear boundaries are established indicating the limits to permissible growth in vitro, and measures are devised to help insure that these limits are respected.
  - c. Guidelines are established regarding permissible and impermissible sorts of experiments. These guidelines should prohibit forming man-animal hybrid embryos.

Respectfully submitted,

*Leon R. Kass*  
Leon R. Kass, M.D.

## FOOTNOTES

1. This paper has been prepared for the Ethics Advisory Board of the U.S. Department of Health, Education, and Welfare. Copyright is retained by the author, and any use of the paper by anyone other than the Board requires consent of the author. Dr. Kass is the Henry R. Luce Professor of the Liberal Arts of Human Biology, The University of Chicago.
2. LeRoy Walters, "Ethical Issues in Human in vitro Fertilization and Research Involving Early Human Embryos," Report to the Ethics Advisory Board, September 8, 1978.
3. "Making Babies - the new biology and the 'old' morality," The Public Interest, Number 26, Winter, 1972, pp. 18-56. It has been pointed out to me by an astute colleague that the tone of the present article is less passionate and more accommodating (or resigned) than the first, which changes he regards as an ironic demonstration of the inexorable way in which we get used to and accept our technological nightmares.
4. In the British procedure, several eggs are taken from each woman and fertilized, to increase the chance of success, but only one embryo is transferred for implantation. In Dr. Soupart's proposed experiments, as the embryos will be produced only for the purpose of research and not for transfer, all of them will be discarded or destroyed.
5. A perhaps justifiable exception would be the case of a universal plague on childbirth, say, because of some epidemic that fatally attacks all fetuses in utero at age 5 months. Faced with the prospect of the end of the race, might we not condone the deliberate institution of pregnancies to provide fetuses for research, in the hope of finding a diagnosis and remedy for this catastrophic blight?
6. Peter Gwynne, "Was the Birth of Louise Brown Only a Happy Accident?" Science Digest, October, 1978. Emphasis added.
7. For the supporting analysis of the concept of "viability," see my arti-



cle, "Determining Death and Viability in Fetuses and Abortuses," prepared for the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, published in Appendix: Research on the Fetus, U. S. Department of Health, Education, and Welfare, DHEW Publ. No. (OS) 76-128, 1975.

8. Some people have suggested that the embryo be regarded like a vital organ, salvaged from a newly dead corpse, usable for transplantation or research, and that its donation by egg and sperm donors be governed by the Uniform Anatomical Gift Act which legitimates pre-mortem consent for organ donation upon death. But though this acknowledges that embryos are not things, it is mistaken in treating embryos as mere organs, thereby overlooking that they are early stages of a complete, whole, human being. The Uniform Anatomical Gift Act does not apply to, nor should it be stretched to cover, donation of gonads, gametes, and (especially) zygotes and embryos.

9. There is a good chance that the problem of surplus embryos may be avoidable, for purely technical reasons. Some researchers believe that the uterine receptivity to the transferred embryo might be reduced during the particular menstrual cycle in which the ova are obtained, because of the hormones given to induce super-ovulation. They propose that the harvested eggs be frozen, and then defrosted one at a time each month for fertilization, culture, and transfer until pregnancy is achieved. By refusing to fertilize all the eggs at once--i.e., not placing all one's eggs in one uterine cycle--there will not be surplus embryos, but at most only surplus eggs. This change in the procedure would make the demise of unimplanted embryos exactly analogous to the "natural" embryonic loss in ordinary reproduction.

10. There is in the literature on interventions in reproduction, no more confused or confusing matter than the meanings of "nature" or "the natural," and its significance for the ethical issues. Its importance is unfortunately matched only by the sloppiness of the treatment in most of the



literature, including, I must add, in my own published writings. It may be as much a mistake to claim that the "the natural" has no moral force as to suggest that the natural way is best, because natural. Though shallow and slippery thought about nature, and its relation to "good," is a likely source of these confusions, the nature of nature may itself be elusive, making it difficult even for careful thought to capture what is natural.

11. An unmarried woman in Dearborn, Michigan, offered to bear a child for her married friend, infertile because of a hysterectomy. She was impregnated by artificial insemination using semen produced by her friend's husband, his wife performing the injection. The threesome lived together all during the pregnancy. The child was delivered at birth by the biological-and-gestational mother to the wife-and-rearing-mother. The first (pregnancy) mother reports no feelings of attachment to the child she carried and bore. Everyone is reportedly delighted with the events. The trio has publicized its accomplishment and is reported to be considering selling rights to the story for a TV show, a book and a movie. Their attorney has been swamped with letters requesting similar surrogate "mothers." (American Medical News, July 28, 1978, pp. 11-12)

12. There are today numerous suits pending, throughout the United States, because of artificial insemination with donor semen (AID). Following divorce, the ex-husbands are refusing child support for AID children, claiming minimally, no paternity, or maximally, that the child was the fruit of an adulterous "union." In fact, a few states still treat AID as adultery. Other suits, such as the following bizarre instance, reveal the importance of preserving the anonymity of the semen-donor. A woman wanted to have a child, but abhorred the thought of marriage or of sexual relations with men. She learned a do-it-yourself technique of artificial insemination, and persuaded a male acquaintance to donate his semen. Now, some ten years after this virgin's birth, the case has gone to court. The semen donor is suing for visitation privileges, to see his son.

13. To those who point out that the bond between sexuality and procreation has already been effectively and premanently cleaved by "the pill," and that this is therefore an idle worry in the case of in vitro fertilization, it must be said that the pill provides only sex without babies. Now the other shoe drops: babies without sex.

14. Science 202:5, October 6, 1978.

15. See "Making Babies - the new biology and the 'old' morality," pp. 19-20. See also my "Regarding the End of Medicine and the Pursuit of Health," The Public Interest, Number 40, Summer, 1975, especially pp. 11-18, and 33-35.

16. There has been much objection, largely from the scientific community, to the phrase "test-tube baby." More than one commentator has deplored the exploitation of its "flesh creeping" connotations. They point out that a flat petri-dish is used, not a test-tube--as if that mattered--and that the embryo spends but a few days in the dish. But they don't ask why the term "test-tube baby" remains the popular designation, and whether it does not embody more of the deeper truth than a more accurate, laboratory appellation. If the decisive difference is between "in the womb" or "in the lab," the popular designation conveys it (see 'Afterword', below). And it is also right on target, and puts us on notice, if the justification for the present laboratory procedures tacitly also justifies the future extensions, including full ectogenesis--say, if that were the only way a womb-less woman could have a child of her own, without renting a human womb from a surrogate bearer.

17. This figure is calculated from estimates that between 10-15% of all couples are involuntarily infertile, and that in more than half of these cases the cause is in the female. Blocked oviducts account for perhaps 20% of the female causes of infertility. Perhaps 50% of these women might be helped to have a child by means of reconstructive surgery on the oviducts; the remainder could conceive only with the aid of laboratory fertilization and embryo transfer. These estimates do not include

(i) additional candidates with uterine disease (who could "conceive" only by embryo transfer to surrogate-gestators), (ii) those with ovarian dysfunction who would need egg donation as well, and (iii) that growing population of women who have had tubal ligations and who could later turn to in vitro fertilization. It is also worth noting that not all the infertile couples are childless; indeed, a surprising number are seeking to enlarge an existing family.





Footnotes

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The Public Interest, Number 26, Winter, 1972, pp. 18-56. See especially pp. 18-23, 32-39, 45 (par. 2) -56.
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7. There is, in the literature on interventions in reproduction, no more confused or confusing matter than the meanings of "nature" or "the natural," and its significance for the ethical issues. Its importance is unfortunately matched only by the sloppiness of its treatment in most of the literature, including, I must add, in my own published writings. LeRoy Walters' discussion of the literature on this question (op. cit., pp. 8-10) points to - - and illustrates - - how much more thought and clarity are needed about "the natural."

IN VITRO FERTILIZATION: SENSE AND NONSENSE  
and a REPLY TO LEON KASS

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Although the literature on in vitro fertilization (IVF) is slim, it is fattening fast, and the ethical issues associated with the use of this technique are now the focus of debates in small professional circles, widespread public hearings under the auspices of the federal government, and just about everything between. We have a clear picture of what the technique is, what can be done with it in the near future, and what further information about the effects of its use we would like to have. We also have a clear picture of what ethical issues are involved in the current debates.<sup>2</sup> What is primarily unclear is how to resolve those issues or, failing their resolution, how to set public policy regarding IVF notwithstanding the likely continuation of unresolved ethical debate.

My objective here is to contribute to that process of policy formulation by calling attention to a few issues that have heretofore been neglected in the literature, and, primarily, by discussing the difference between good and bad arguments in the on-going debate. I will offer some concluding remarks about what I believe the policy of the federal government should be in regard to IVF in both clinical and experimental settings, but those remarks will be offered at less length and with less confident conviction than the intervening discussion of good and bad arguments.

1. The status of the embryo. There is a crucial conceptual distinction, too often lost sight of, between facts that we may seek

to discover and decisions that we need to make. What function a particular enzyme serves is a fact. If we wish to know that fact, we seek to discover it through an appropriate program of research. Contrast that situation with the question of when a young person becomes an adult. That a young person warrants classification as an adult at 13 or at 18 or 21 is not a fact to be discovered through research in biology, physiology, psychology, or anything else. It is a result of social policy, a decision of the body politic. This distinction between facts and decisions seems clear and straightforward, yet sometimes the two categories become confused. Perhaps the most widely known example of such confusion has to do with the definition of death. There has been a great deal of recent discussion about when death may be said to have occurred. Some of that discussion proceeds on the apparent misconception that the true criterion of death is a fact to discover. Yet what the appropriate criterion of death should be in clinical situations is not a fact to discover, it is a social policy to make.<sup>3</sup> That is one reason why the results of such discussions are somewhat unstable -- why the question of the criterion of death is a subject of on-going dispute; the factors that go into justifying a social policy decision are always open to review and to argument.

In the debate about IVF, much attention is focused on the question of the status of the embryo -- both the embryo that is implanted and the embryo that is dealt with in some other way. Inevitably questions arise of whether or not such embryos are persons or, persons or not, are the bearers of rights. These are not questions

of fact, but like the question of the criterion of death, are questions requiring the setting of a social policy.

To say of such questions that they are questions of policy is not to say that the answers are unconstrained. There are clear cases of life and of death; the question arises -- and a policy is needed -- only in those cases at the margin where some physiological systems still function while others are irretrievably lost. So the range within which decision can be made is rather narrow. Similarly, the questions of what to count as a person and what to count as a bearer of rights require decision only within a circumscribed range -- the cases at the margins of personhood. Such cases are of various sorts -- the anacephalic newborn, the linguistically proficient primate, the embryo.

The setting of policy on the question of humanization, of what counts as a person, can go awry, as it did in the context of American slavery. That institution was justified by some defenders on the grounds that slaves, though humanoid, were not persons. Their criterion of personhood, facile and self-serving, was based on an irrelevant characteristic -- skin color -- and hence was simply erroneous. There was nothing marginal about the humanity of kidnapped Africans. But to say that American slavelords made the decision wrongly, indefensibly, is not to undermine the view that what is to count as a person is, at the margin, still a policy decision to make. The point is that it must be made on a morally relevant basis.

I will not rehearse here the extensive debate about the personhood of embryos and fetuses, a debate that has been fueled by intense

division of sentiment about abortion. Rather, I will simply sketch the conclusions that seem to me to provide the most defensible basis for public policy, as contrasted with personal moral choice.

Surely the concept of a person involves in some fundamental way the capacity for sentience, for an awareness of sensations at the very least. In the normal case, of course, there is much more. There is self-awareness, capacity for reflection, a sense of others and of relationships between self and others. So the condition of sentience is a very weak one, a necessary condition for personhood, but far from a sufficient condition.

No one seriously contends that embryos are sentient, that they are capable of even the slightest awareness of pleasure or pain. Of course, if all goes well, they will develop into people, and it is on that potential that the case for personhood largely rests.

The idea of potential is a tricky one. We often hear encomiums to it; individuals should have the opportunity to fulfill their potential, it is somehow grounds for disappointment when someone fails to live up to his potential, and the like. But that is all very sloppy talk. For some potentials are desirable and others are not. He who has the potential to be Sherlock Holmes has the potential to be a master criminal; she who has the manual dexterity for neurosurgery perhaps has the potential to be a leading pickpocket as well. Further, he who has the potential to be a weight-lifter and to be a ballet dancer must choose between them; what advances one potential interferes with the other. So aphorisms about potential are elliptical; in fact, they are elliptical for tautologies. It is good to advance those potentials



that it is good to advance.

Even if it is true that people should be allowed, encouraged, or assisted in living up to some of their more desirable potentials, we cannot use that principle in defense of a claim that embryos have personhood or rights, since that principle is about the potentials of persons -- and whether embryos should be accorded the status of persons is precisely the point in question. It is not at all obvious that rights should accrue to an object just because it has the potential, assuming that all goes well, to become a person at some later time. Indeed, the unfertilized human egg, like the embryo, has the potential to become a person if all goes well. And no one has argued that each unfertilized egg, or each spermatozoon for that matter, be accorded personhood or rights. One does hear it said of the embryo that it has not merely the potential to become an adult person, but the potential to become a particular adult person. Its genetic identity is complete; it is already a unique individual. That does distinguish it from spermatazoa and ova in isolation. But that does not distinguish embryos from unjoined pairs of sperm and egg. That no union has yet occurred does not alter the fact that any pair of sperm and egg have the potential, if all goes well, to become a genetically specific adult person. The point of conception may be, for some, a convenient place to draw the line, but there should be no mistake about the fact that it is drawn there for convenience. That is no less "arbitrary" a choice than the choice to draw the line later, which on grounds of policy considerations it may make better sense to do.

If we come at the problem from the other end, we cannot help but be struck by the similarity between infants and late stage fetuses. Indeed, the late stage fetus is not only clearly sentient, reacting to stimuli in its environment. In many or most cases it already holds a place, as a specific though as yet unseen individual, in a network of human emotions and expectations. In most respects it is like a child, and utterly unlike an embryo.

For my part, the onset of the capacity for sentience marks a qualitative change in the development of the fetus. From that point forward, what we do in regard to it may cause it, as a present actuality, to suffer harm. Surely this is a morally significant factor, though of course it is not the only one, and may often not be a dominant one. It is an empirical question of neurological development when that change occurs; it happens sometime prior to quickening but well after the embryonic stage. That we have no word for this event, this point in the series of events that includes conception, quickening, and birth, reflects only the fact that we have not historically invested it with much significance. It is not necessarily any the less significant for that.

The later it is in its development, the more seriously we should take a fetus as a person in the making. I see no reason for, and no possibility of, holding to a clear cut distinction between the non-person and the person in this regard as if personhood snaps into place in an instant, instead of emerging organically out of a developmental process. That emergence, I suggest, begins to have moral force with the onset of fetal sentience. In any case, I know of no persuasive

arguments for the position that the most reasonable social policy is to accord the embryo the status of a person.

2. Doing harm. Some discussions of the ethics of IVF focus on the prospect of harming embryos as a result of IVF.<sup>4</sup> It is worth noting that sometimes events can be properly understood -- even properly described -- only in retrospect. If a physician damages an embryo with the subsequent result being the birth of a malformed child, that embryo at the time of the damage, because of its subsequent historical connection with the child, has a different status than it would have had if it had only been used in short term research. Further, that physician's action bears a different relationship to the interests of persons. If a physician negligently or willfully damages an embryo which as a result later develops into a malformed person, it is appropriate to say that the physician's action at the time constituted an injury to someone, with all that entails about culpability and liability. But if the embryo does not develop to the point at which substantial personhood has emerged, it will likely be inappropriate to say that the physician's action was an instance of damaging someone -- however open to criticism it might be on other grounds. In some situations, we cannot be completely clear about the status of an event or action without taking into consideration some of the subsequent resulting events.

There is a likelihood of unknown magnitude that some children born as a result of clinical IVF will be defective. The defects may or may not result from the use of IVF. There are two extreme views about responsibility related to such defects. The first view suggests



a sort of strict liability. Thus, Tabitha Powledge, in an article basically sympathetic to the clinical use of IVF, writes:

What should be made completely clear to people contemplating in vitro fertilization is that there is risk, if of magnitude unknown at the moment. Advance arrangements -- especially financial ones -- should be made for coping with a malformed baby.<sup>5</sup>

On this view, one who wishes to proceed with this sort of undertaking must virtually post bond against the possibility of defect. The opposite view, that of a kind of strict immunity, is suggested, though not advocated, by LeRoy Walters. He asks:

Would one want to exclude all products of in vitro fertilization from the class of subjects eligible for compensation -- at least for injuries apparently caused by the IVF and embryo transfer procedure?<sup>6</sup>

On this view there is a certain risk present in any sort of reproduction, and physicians should have no responsibility for untoward consequences.

Both views seem clearly wrong. In the clinical use of IVF, negligence is possible, and there is no reason to provide immunity to those whose negligence or possibly even willful malfeasance lead to disastrous consequences. Of course, damage or defect are not themselves proof of any culpability, and hence it would require strong evidence to support a claim that there was liability associated with a defective birth.

On the other side, there seems no adequate reason to consider our commitment to defective IVF neonates, whether the defect is IVF related or not, to be any different from our commitment to defective neonates generally. There is risk in the normal pregnancy, and in some cases it is known in advance for genetic or other reasons that



there is heightened risk, yet we do not require the posting of bond. Perhaps it may be said that we do so, albeit inadequately, collectively through the existence of public institutions for custodial care, medical insurance programs, and other social constructs. If that suffices for other cases, it should suffice for IVF cases. If not, the inadequacies have no dependence on problems essentially associated with IVF. In fact, the treatment of seriously defective newborns is a particularly difficult problem. R. Duff and A. G. M. Campbell, in their courageous and forthright discussion of the deliberate termination of life in cases of neonatal monstrosity, remind us of the difficulty of this issue, which far transcends the problems particularly associated with IVF.<sup>7</sup>

Professor Paul Ramsey, the leading Cassandra among the commentators on IVF, makes much of a principle he calls one of "the received principles of medical ethics," the principle "Do no harm."<sup>8</sup> It is not obvious how one should interpret that principle. Taking it literally is indefensible, since physicians cannot avoid doing harm to some extent, and it is futile at best to admonish people not to do what they cannot avoid doing. What are some possible interpretations of the principle that are more plausible? (a) "Intend no harm." That interpretation makes no useful distinctions for us. None of the proponents of IVF in research or therapy intend harm. (b) "Do no harm on balance, all things considered." This interpretation is little better. Only thoroughly incompetent physicians do more harm than good. They exist, but that is a problem unrelated to our present concerns. (c) "Risk no harm." This interpretation would shut down the major portion of

medical practice. Physicians unavoidably risk harm in nearly all they do.

In sum, the principle "Do no harm," which is much lauded in the literature and on which Professor Ramsey bases a good deal of his argumentation, is discredited by serious reflection. Physicians do harm, and in enormous amounts. One Public Health Service official has estimated that one hospital day in seven is a result of some iatrogenic illness or injury.<sup>9</sup> But the harm that physicians do is often an essential part of the good that they do. A principle, if it is to be useful in support of an argument, must help us make distinctions. The "Do no harm" principle fails to meet this standard, however useful it may be in engendering an aura of beneficence within and about the medical community.

Professor Leon Kass also makes much of the "Do no harm" principle in his gloomy discussions of IVF. Referring to it as "the minimal principle of medical practice", he has cited it in an argument to the effect that research in IVF should be suspended until the safety of such research is totally assured.<sup>10</sup> Such a moratorium, however, would in fact be a categorical prohibition, not just on IVF research or therapy, but on medical research, and indeed, on most medical therapy in general. For where there is research, there is necessarily ignorance. In the absence of ignorance, it would not be possible to conduct research at all. And where there is ignorance, there is always risk.<sup>11</sup> To insist on a criterion of assured safety is to insist on the absence of risk, and to do that is to insist on the absence of research altogether. Further, since medical therapy is almost

always an experiment on the patient, clinical intervention is almost never risk-free, and would also be prohibited by a policy that bases a no-risk standard on the "Do no harm" principle. Professor Kass anticipates this objection, but his effort to thwart it misses the mark. For his discussion shifts at that point to questions of consent, which, he rightly observes, the IVF embryo cannot provide. But he says nothing to illuminate the mystery of why consent or its absence are even relevant to the justifiability of risk when the minimal principle of medical practice categorically prohibits doing harm. This quest for assurance is futile. It is futile in epistemology, futile in ethics, and futile in research and therapy. As A. J. Ayer points out in discussing the concept of rationality, it is not irrational to accept less than total assurance. What is irrational is to insist on a guarantee where none can be forthcoming.<sup>12</sup>

The problem then is not to avoid risk absolutely, but to make one's peace with the fallibility of judgment and of action, and to begin to make discriminations among risks and harms. The issue that must be addressed is that of which risks are worth undertaking, and which harms worth enduring, for which purposes.

3. Slippery slopes. Laced through the literature of objection to IVF therapy and research is what has variously been called the slippery slope argument, the camel's nose in the tent argument. As a skier, I prefer to think of it as the slippery slope argument. The structure of the argument is surely familiar: once one starts sliding down a slippery slope, things get out of control. There is no stopping; disaster awaits us. To my knowledge, no skier thinks the argument is



good. Fortunately, it is possible to start down a slippery slope and then to stop. If that were not possible, a major recreational industry would shut down at once.

Professor Ramsey's apocalyptic prose assures us of disaster. He claims that such measures as artificial insemination and in vitro fertilization are the first steps down the garden path, the first bits of skid down the slippery slope; and there is in Ramsey's view no slowing up, no turning back.<sup>13</sup> But whether that view is reasonable or not is surely a straightforwardly empirical question. Some processes are such that, once begun, it is difficult or impossible to stop them. Others are not, and it is always an empirical question which sort we are talking about in any given instance.

I will not attempt to ski down the Schilthorn, though I have seen others do it. I will not attempt it, because my descent, once begun on that insanely precipitous slope, would surely terminate only in disaster below. I might as well attempt to ski to safety from a plane in flight. Given my skiing ability, the slippery slope argument against my attempting that slope is sound. Yet I can easily handle some slopes that beginning skiers properly shun. It is a question of control and, in part, of judgment.

Is the slippery slope argument against IVF a good one? It is not enough to show that disaster can be expected if the process is not controlled. A man walking East in Omaha will drown in the Atlantic if he does not stop. The slippery slope argument against IVF must also rest on evidence about the likelihood that judgment and control will be exercised responsibly. Here is where Ramsey's argument collapses; he describes disaster, and rests his argument on the



impressively pessimistic assumption that such unhappy outcomes as are possible will surely occur. But there is no reason to take such a position seriously. Collectively, we do have a significant capacity to exercise judgment and control. We have not always done so as well as one might hope, but our record is actually rather good in regard to questions that arise in respect to medical treatment and research. Consider, as a case in point, the vexsome problem of abortion. Some opponents of a liberal abortion law argued against a liberalization on the ground that once we allow the killing of fetuses, no way can be found to stop the slide down the slippery slope. If we sanction abortion, even where amniocentosis reveals a defect like trisomy 21, there is no justification for not sanctioning infanticide as well. For gross malformation is a feature of neonatal intensive care, and if we would sanction aborting a fetus on the grounds that it is going to be seriously defective, why not sanction infanticide on the grounds that the child actually has the dreaded defect? Further, such infanticide is just a short skid away from the killing of those judged socially useless, so that if one sanctions early term abortions even in cases of demonstrable defect, one has irretrievably opened the floodgates to the selective slaughter of anyone in social disfavor.

It is clear that no such disaster has ensued. A process of social policy determination has exercised judgment. It is a judgment that has made a lot of people on both sides unhappy, but it is nonetheless a judgment that makes clear that we can stop a process once we have begun it. Anyone who has ever had a haircut should know that, too.

There are many other examples of our capacity to exercise judgment. Consider Willard Gaylin's concept of the neomort -- the irretrievably comatose individual declared dead but kept respirating -- quasi-alive -- with artificial life support systems in order to be used as an organ bank or research subject.<sup>14</sup> The only significant social consequence of that notion so far is that it prompted Robin Cook to write the novel Coma.<sup>15</sup> It certainly has not resulted in any change in attitude toward the treatment of terminally ill patients. Or consider an experiment in language acquisition and early child development. We could learn a great deal by raising some children in strict isolation from all linguistic input for three or four years, and then immersing them in a highly verbal environment. No one denies that would be a scientifically sound and useful experiment, but nobody proposes doing it. We do not and will not do such experiments because we have the capacity to judge that on ethical grounds they are indefensible. Andre Hellegers and Richard McCormick are right when they speak of "benefits we can never enjoy because we cannot get them without being unethical."<sup>16</sup> There is a difference, despite the fears of the pessimists, between what we could do and what we do, and that difference is to a large extent due to our capacity for judgment.

It is important to note that with regard to IVF applications, we do not face any single slippery slope argument. Rather, there are several. There is the argument that clinical IVF poses a threat to marriage and the family, or to mankind's self-image, and there is the quite separate argument that IVF research will lead to experimentation of an ethically undesirable sort on late-stage fetuses. Each such

consideration involves an empirical assessment of the likelihood that sound judgment will prevail as well as an assessment of the magnitude of the disaster that will ensue if it does not. I will return to one of these arguments below.

Finally it is important to acknowledge a point about slippery slope arguments emphasized by Dr. Kass.<sup>17</sup> The likelihood of the subsequent exercise of judgment and restraint may largely depend on the principles that are used to justify first steps. If early term abortion were justified by the principle that parents enjoy absolute dominion over their issue, the adoption of that principle would already have constituted a sanctioning of infanticide. If IVF research on embryos is justified by the principle that pre-natal fetal life is of no moral consequence, there will be no basis for restraint in regard to research on later stage fetuses. So it can matter a great deal how the justification of first steps is formulated.

4. Naturalness. The concept of what is natural plays a prominent role in the reasoning of Professor Ramsey, and to some extent of others as well. Ramsey writes:

Today many are testifying to the spiritual autonomy of all natural objects and to arrogance over none; to the scheme of things in which man has his place. But there is as yet no discernable evidence that we are recovering a sense for man as a natural object, too, toward whom a like form of "natural piety" is appropriate....procreation, parenthood, is certainly one of those "courses of action" natural to man, which cannot without violation be disassembled and put together again -- any more than we have the wisdom or the right impiously to destroy the environment of which we are a part rather than working according to its lineaments, according to the functions we discover to be the case in the whole assemblage of natural objects.<sup>18</sup>



He then goes on to advocate

...the view that the proper objective of medicine is to serve and care for man as a natural object, to help in all our natural "courses of action," to tend the garden of our creation.<sup>19</sup>

It is long past the time that this sort of argument were laid permanently to rest. That something is natural or is not has, by itself, absolutely no moral force. We can distinguish three senses in which an action or process can be said to be natural. Consider each in turn.

(a) It conforms to the laws of nature; the contrast, I presume, is with the impossible or with the supernatural. Everything we do or could do -- the good and bad alike -- is natural in this sense. No moral distinctions can be based on it.

(b) It is free of human intervention; the contrast is with processes influenced by mankind's efforts to manipulate his environment. Nothing we do is natural in this sense, for our action is itself the mark of the unnatural. Surely the practice of medicine is as clear an example as one could imagine of human efforts to manipulate the playing out of events, as when we deliberately destroy "natural" life forms, and terminate a "natural" process, by using antibiotics to cure an infection. No moral distinctions can be based on this sense of what is natural either.

(c) It conforms to some natural moral law or other code or set or principles of value; the contrast here is with what is wrong, what is a violation of principles about how one ought to act. On this interpretation, the concept of what is natural has moral force, but only because it is itself based on some prior judgment about what is right and what is wrong -- a judgment that is then reflected in the



choice of what to call natural and what to call artificial.

The passage from Ramsey suggests that it is the third sense of 'natural' that he employs; that he sees certain processes, such as normal procreation, as desirable, and that he extols their naturalness without thereby suggesting that medical intervention is typically a violation of nature. The claim of naturalness is thus a moral conclusion, not evidence that can be offered in a moral argument. The real distinction that is operating in the argument is the distinction between what is desirable and what is not. Professor Ramsey sees atypical reproduction as undesirable, but he says little about why, and his invocation of the concept of the natural only obscures the point that there is the morally desirable and the morally undesirable, and we must make judgments on the basis of the difference between them, not on purported grounds of naturalness. I do not understand why this confusion persists as widely as it does.

5. The function of medicine. Both Professor Kass and Dr. R. G. Edwards, in his reply, have discussed the proper function of medicine and whether IVF is defensible in terms of the proper function of medicine. There are some serious issues here, especially as we bear in mind the increasing government involvement in health care financing. Kass argues:

Just as infertility is not a disease, so providing a child by artificial means to a woman with blocked oviducts is not treatment....What is being "treated" is her desire -- a perfectly normal and unobjectionable desire -- to bear a child.<sup>20</sup>

Ramsey voices a similar concern:

The important line lies between doctoring desires...and seeking to correct a medical condition if it is possible

to do so....medical practice loses its way into an entirely different human activity -- manufacture...if it undertakes either to produce a child without curing infertility as a condition or to produce simply the desired sort of child.<sup>21</sup>

Edwards replies:

A great many medical advances depend on the replacement of a deficient compound or an organ. Examples include insulin, false teeth, and spectacles: the clinical condition itself remains, but treatment modifies its expression. Patients taking advantage of these three treatments are surely receiving the correct therapeutic measures, the doctors treating the desire to be nondiabetic or to see and eat properly... Exactly the same argument applies to the cure of infertility: should patients have their desired children, the treatment would have achieved its purpose.<sup>22</sup>

We need not rely on the idea of prosthetic devices to make Edwards' point that treatment does often leave the initial condition unaltered while responding to a patient's desire somehow to transcend the limitations imposed by that condition. Certainly the administration of tranquilizers, sleeping pills, and analgesics are examples of medical treatments which do not correct physiological deficiencies, but respond, in a sense, to a patient's desires. So Edwards' defense seems adequate. Treating some desires is a traditional and appropriate part of medical practice.

But the problem runs deeper than that, for it is not clear that it is appropriate to treat all medically treatable desires. First, there is the question of the distribution of costs, a question that has heightened impact if we consider the use of public funds to underwrite the costs of medical treatment. It is one thing to provide insulin, dialysis or dentures to a patient. But should we provide cosmetic surgery, such as that obtained by Betty Ford, where the desire does not arise out of any injury or illness, but rather is simply a

wish to be more youthfully attractive? Perhaps such treatment is unexceptionable, at least if the costs are borne wholly by the patient rather than by a medical insurance fund or by other means of cost distribution. But other desires arising out of vanity seem less legitimate. Should surgical treatment have been available at all to those women who, in the 1950's, had their little toes amputated in order to fit their feet into narrower and hence, in their benighted judgment, more fashionable shoes? Or is the provision of such treatment perhaps a misuse of medical skills, a perversion of the privilege that the license to practice medicine signifies? I submit that this is the case, and that the underlying reason is that the treatment of a desire for self-mutilation in the service of a whimsical vanity is not the sort of desire that legitimately warrants treatment.

The point here is that value-free medicine is not fully possible. Some judgments must be made about which desires are properly treatable and which not. We cannot oppose clinical use of IVF on the grounds that it is the treatment of a desire, nor can we simply approve it on the grounds, as Edwards suggests, that the treatment of desires is medically legitimate. Rather, we must face directly the question whether the desire to have a child of one's own, when IVF is the only available remedy, is one of the desires that warrants medical response.

6. Marriage and the family. There has been considerable speculation about the impact of clinical IVF on marriage and the family. Some of the prognostications are dire indeed. Andre Hellegers and Richard McCormick warn of the procedure toward which they see IVF leading:



We see in these procedures grave assaults on marriage and the family, to say nothing of the subtle devaluation of sexual intimacy that clings to them.<sup>23</sup>

But, whereas they raise concerns, and call for "a serious public discussion," Professor Ramsey speaks of "what the manipulation of embryos will surely do to ourselves and our progeny."<sup>24</sup> He goes on to invoke the chilling images of a Huxlean world in which "there is no poetry."<sup>25</sup>

It is well that these issues have been raised, for they are of the first importance. But it is necessary not to lose sight, in the glare of that undeniable importance, of the need to examine the evidence. What reason is there to give credence to portents of familial disaster? Much of the case seems to be based on concern about the separation of reproduction from sexual intercourse. But artificial insemination, both with husbands' sperm and with donors' sperm, has been practiced fairly widely, if not very visibly, for decades. There has been no discernible deleterious effect on marriage or the family. More importantly, the wide availability of inexpensive and effective methods of birth control means that, for the first time in human history, sex and reproduction have in fact already been separated in a large scale way. The impact on social structure will surely be astounding; I have no doubt it will transcend our current understanding. So it is a wholly idle worry that IVF will separate sex and procreation.

It is worth remembering, moreover, that IVF involves hospitalization and surgery, and it is a very small percentage of the population that is in any position to benefit from it. The traditional method of conception will remain the method of choice. It is inexpensive,



can be performed at home, takes little time, even less skill, and is a great deal of fun. I do not see it as being in serious jeopardy.

Further, we are only beginning to document what we have known all along, that there is no substitute for early parent-child interaction. The work of Klaus and Kennell on mother-infant bonding is a case in point.<sup>26</sup> As we come to understand more fully how the family works when it is working well, I suspect that our appreciation of it and of its special capacity for nurturance will grow. I agree entirely with Hellegers and McCormick that we should take the long view and that we should look at societal consequences, not simply individual needs, in evaluating IVF. But I do not see that the family is under grave assault because of IVF. Indeed, it is often a respect for family, lineage, and the traditional parental role that prompts the request for clinical IVF in the first place.

Finally, mankind's image of what it is to be human may well involve a sense of lineage and of parenting, and that image may undergo some perturbation from the few cases in which procreation has a heavy dose of technology added. But mankind's sense of what it is to be human is threatened far more seriously on other fronts. Recent work on primate language acquisition has stripped us of the illusion that we alone have the capacity for abstraction or to communicate to others a sense of self-awareness, and in the process the sharpness of the distinction between humans and the higher primates has been blunted.<sup>27</sup> Recent work in artificial intelligence has produced machines with awesome cognitive capacities, and the sharpness of the distinction between people and machines has also been blunted.<sup>28</sup> We have ample

reason to reflect seriously about what we are, and the prospects for IVF add little to the case.

7. The burden of proof. Nowhere in the literature have I found any consideration of where the burden of proof does or should lie in regard to the justifiability of using IVF. This is a startling fact, for it makes a great deal of difference what the answer is. Consider first the case of research. In the normal course of events, a scholar in any of the traditional disciplines within the arts and sciences may pursue whatever topic of research he chooses, using, unchallenged, whatever techniques are available to advance that pursuit. Of course, that freedom does not entail any entitlement to support for the research, nor to respect for its outcome. Those quite properly depend on the merits of the work. Only when the research involves experimentation on sentient beings -- humans and animals -- do restrictions appear on the scene. Then, the researcher must satisfy certain entirely reasonable conditions aimed (with arguable success) at ensuring humane and decent treatment of those subjects. Of course, one might object on moral grounds that certain research should be stopped even though no experimentation on sentient creatures is involved. But in such a case the burden of proof clearly rests with the opponent. Unless he can provide a convincing argument on the side of the prohibition, the work may proceed. And such a burden is rarely borne with success.

Since research employing IVF does not necessarily involve any experimentation on sentient creatures, it would seem that no general prohibition against such research is supportable except by arguments on the merits of the case. Of course, where sentient subjects are

involved, the normal requirements would apply.

But if, for some reason as yet unspecified, the proponents of IVF research must justify their work as a precondition for undertaking it, the logic of the situation changes. The opponents then become critics of the justification -- a much easier burden to bear than that of demonstrating the case for prohibition. So it matters quite a lot whether the burden of justification rests on the side of the proponents or of the opponents.

Now let us consider clinical situations. In order for a drug to be available for clinical use it must have been shown, under difficult and constrained experimental circumstances, to meet fairly stringent standards of safety and effectiveness. The burden of proof clearly rests with the proponent of the use of a new drug, and the difficulty of bearing that burden has been decried by some as a barrier to medical progress. The situation is entirely different with regard to new surgical techniques. Almost no standards constrain the introduction or use of surgical procedures -- even those that have come under heavy attack in the medical literature. The burden of proof clearly rests with the opponents of a surgical technique, and the difficulty of bearing that burden has been decried by some as a barrier to the control of dangerous practices. It would be a different world if it were the opponents of the use of a drug, or the advocates of the use of a surgical technique, who had to demonstrate the worth of their case.

The clinical use of IVF is basically a form of surgical intervention -- typically a laparoscopy followed by some laboratory work



followed by surgical implantation of an embryo. As such, it needs no special justification, and physicians are at liberty to employ it in accordance with their clinical judgment. Those who would prohibit the procedure have two options. Either they must show, on the merits of the case, that the prohibition is justified, or else they must show that the burden rests with the advocates of the procedure to demonstrate its acceptability. If they can succeed in the latter course, they are spared the difficulty of the former. Thus, again, it matters where the burden lies..

I have spoken of advocacy and of prohibition. But the real situation, especially in regard to government policy, is more complex. The government can prohibit a practice through legislation, can discourage it -- almost to the point of prohibition -- through regulatory rulings, can be neutral in regard to it, can encourage it by making federal support available, or can bring it about indirectly through contracted extra-mural programs or directly through intra-mural programs. Charting the best course of action among all these options -- over both clinical practices and a diverse range of research prospects -- will require a careful separation of the good arguments from the bad. What counts as a good argument, however, often depends on who bears the responsibility of proving what. Thus the question of what the various burdens of proof and justification are, and where they do and should lie, ought not be ignored. Thus far, in the debate about IVF, there seems to be an implicit acceptance in most of the literature that the opponents of the research and the therapy need to demonstrate their case. It is a separate question, of course, whether that burden



can or cannot be borne. And some have pointed out that it is also a separate question whether that is where the burden should lie.

8. Consensus. Marc Lappé has argued:

The moral issue of human embryo manipulation is so great and of such importance to the course of the history of man, that nothing short of a consensus of the scientific communities involved would be needed before proceeding.<sup>29</sup>

But given the moral pluralism that we enjoy or from which we suffer -- opinion is divided on that -- Lappé's view amounts to an affirmation of the status quo ante. When he speaks of a consensus being required before we proceed, he is speaking -- perhaps unintentionally -- of an absolute ban, for no consensus is possible on an issue of this sort. The absolutists on either side will be unsatisfied with any resolution but their own. Again, I cite as an example our policy with respect to abortion. Those who advocate federally funded abortion on demand without limit of time, and those who oppose abortion categorically, alike maintain a distaste for the Supreme Court decision. A requirement of consensus would have us still adrift without any policy, beyond whatever happened to be in place, about abortion.

To say that the quest for consensus, like the quest for certainty, is hopeless, is not to say that just any policy will do. Even amidst the pluralistic currents of ethical argument, there are constraints on what we can defend morally. At the heart of these constraints are widely shared commitments to fairness, to a respect for persons, and to a derivative respect for the aspirations that people have. We should be guided as well as we can by those moral principles that capture, insofar as possible, the common moral ingredients that exist

within our pluralistic culture. We will find that quite hard enough without insisting on consensus.

9. Allocation of resources. It should be clear at this point that I do not find the standard arguments against clinical IVF to be persuasive. Nor do I know of others that have greater force. But I am not on that account a vigorous advocate of the technique. It is not that, like some, I fear the impact it will have on human population. The numbers will be too small for that to be a serious consideration. Rather, it is a question of priorities in the allocation of resources. In the competition for support, the burden of making a convincing case should rest with the proponents of a given line of work. With forty million Americans having no adequate access to decent health care, with thousands of children born annually without prospect of a family to nurture them, with venereal disease -- a major cause of infertility -- on the rise, it is implausible that research into making IVF more readily and reliably available should be a project of high priority concern. It isn't so much the harm or risk it involves as the plainly greater importance of addressing more fundamental and widespread problems of health and the delivery of health care.

Regarding the use of IVF in research programs aimed not at improving our ability to treat or circumvent infertility, but at increasing our understanding of cell differentiation and other aspects of fetal development, the reasons for restraint are of a quite different sort. For the case can be convincingly made that important knowledge could be gained that would aid in the prevention or correction of serious developmental defects. I am not troubled by such research done on

embryos, subject to conditions given below. But once the first glimmerings of sentience appear, the developing fetus begins to exhibit those characteristics of humanity in virtue of which it is a moral offense to treat persons solely as means in service to the purposes of others. Such research would almost surely involve manipulation of the fetus -- exposing it to various influences of indeterminate effect, trying to induce developmental defects of the sort we seek to understand, and the like -- and the imposition of such assaults on unwitting sentient human life is open to moral objection. Again, there are some useful research projects that should not be undertaken.

10. Recommendations. What sort of regulations should the federal government adopt? What sort of policy should it pursue, in respect to IVF? There should be no legislative or regulatory prohibition against clinical IVF. Its use should be allowable with no special restrictions beyond those which regulate the practice of clinical medicine more generally. But careful records should be kept of all instances -- successful and unsuccessful -- of attempts at clinical IVF, so that a significant body of data about all aspects of the procedure will accumulate. The federal government can certainly catalyze more conscientious record keeping in this instance than the medical profession is typically prone to pursue. But the government should not conduct nor be much sympathetic to supporting programs designed to provide clinical IVF on a more widespread basis.

Research involving unimplanted IVF embryos should not be prohibited by law or regulation, provided that informed consent is obtained from the donors of both sperm and egg, provided that all other require-



ments are met through the Institutional Review Board process, and provided that the research terminates prior to the onset of fetal sentience. Beyond that, notwithstanding what we might learn, such research should be prohibited. Research involving implanted embryos should be considered fully on a par with research involving other instances of pregnancy.

These recommendations are based on the belief that, according to the most reasonable policy decision, the status of the embryo is not equivalent to that of a person, a child, an infant, or a fetus -- at least, a fetus from the point of development of the capacity for even primitive sentience. I am willing to sanction research on embryos because I see no convincing argument against it, and I believe the burden rests with the opposition to show why it must be prohibited. But I see no defense of research on late-stage IVF fetuses -- or of the research it would take for late-stage IVF fetuses even to exist -- even though such research could have great importance. I conclude that a line of acceptability should be drawn that separates these two cases. I would tend to draw that line somewhat conservatively; that is, rather close to the point where cell differentiation begins, rather far from the capacity for independent survival.

Finally, I want to emphasize the value of those essays of which I have been particularly critical. I have focused on those arguments I find inadequate, but the works by such writers as Kass, Hellegers, McCormick and Ramsey raise questions that can too easily be ignored, and their cautionary remarks, even where flawed, perform a public service. For they challenge us to be clear and reflective about



what we are doing. And unless we can face that challenge, we may well blunder into disaster. The fact that our institutions of public policy now conduct broad based and ethically informed discussions before setting policy is due mainly to such efforts as theirs.

### References

1. I am grateful to the members and staff of the Ethics Advisory Board, Department of Health, Education and Welfare, for their interest in and support of the writing of this essay. I also appreciate helpful discussion with Martin Gellert, and comments on an earlier draft made by Ruth Macklin. Both, of course, are wholly innocent of this essay's failings.
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IN VITRO FERTILIZATION AND EMBRYO TRANSFER: FROM  
A PERSPECTIVE OF MORAL THEOLOGY

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This paper will examine the ethical aspects of in vitro fertilization and embryo transfer from the perspective of Roman Catholic moral theology. A preliminary consideration will briefly explain the nature of moral theology and its relationship to other disciplines.

Introduction: Moral Theology. Moral theology in a systematic and thematic way studies human behavior and acts from the perspective of the Roman Catholic faith understanding. There are three distinguishing characteristics of moral theology--a faith perspective and its implications, the use of reason and the teaching role of the church community.

All religious ethics share a dependence on a faith perspective and thus are differentiated from all purely philosophical or rational ethics. Roman Catholic moral theology with its proper faith perspective shares much in common with Jewish ethics and especially with Protestant ethics. The reality of faith shapes the experience of the individual believer, establishes the believing community of the church and finds a privileged written source in the revealed scriptures.

Second, moral theology accepts the importance of human reason and its role as a source of ethical wisdom and knowledge for Christians and for all others. The Catholic tradition has traditionally upheld the principle that faith and reason can never contradict one another. Thomas Aquinas, the most significant figure in the Catholic theological tradition, exemplifies this acceptance of human reason, since he employed the thought of the pagan philosopher Aristotle to understand and express better the Christian faith itself. Catholic moral theology has traditionally given

heavy emphasis to the natural law approach in studying human actions. The natural law is aptly described as human reason directing human beings to our ultimate end in accord with our human nature. Through human reason we share and participate in the reasonable plan of God<sup>1</sup> for the world.

There are many significant theoretical questions about the relationship between faith and reason in moral theology. However, the history of Catholic moral theology indicates that for the most part human reason has been the primary basis for the teaching proposed on medical ethics and on specific moral issues such as in vitro fertilization or artificial insemination.<sup>2</sup> I agree with the position proposed by a good number of contemporary Catholic moral theologians that there is no specifically unique content to Christian ethics which is not<sup>3</sup> available to the experience of all human beings existing in our world.

Appeals to faith can and do shape the general approaches and perspectives which one brings to a particular question. Some perspectives might be incompatible with a faith vision. A Christian faith vision would be wary of any utopian scheme for the ultimate perfection of the human race through science or technology. The Christian vision recognizes the specifically human aspects existing in the innermost depths of the human person--the basic realities of freedom, self-determination, grace and sin. Finitude, evil and death will always characterize human existence, but at the same time the Christian who shares now in the new life of the resurrection should try to overcome sin. However, the fullness of the kingdom will never exist in this world but will always be God's gracious gift at the end of time.

Different emphases within the Christian perspective might result in different attitudes. Christian anthropology allows for different interpretations. Paul Ramsey, a Methodist ethicist, sees in the attempt of human beings to control their human future through genetic manipulation and the alteration of human parenthood the basic sin of pride or <sup>4</sup> hubris--the temptation to play God and to deny our creatureliness. On the other hand, Harvey Cox maintains that the great sin of human beings is not pride but sloth--the refusal to take responsibility for our future <sup>5</sup> life. Likewise, Christian eschatology allows for different perspectives. Ramsey stresses discontinuity between this world and the next and hence is somewhat pessimistic about progress and development in human life. Others, such as Harvey Cox in his earlier writings, see a greater continuity between this world and the next so that they are more optimistic about what human beings can do in the world. Joseph Fletcher, in his writings on bioethics, implicitly accepts an anthropology and eschatology <sup>6</sup> similar to that proposed by Cox.

The reliance on human reason in solving specific ethical questions is well illustrated in the discussion of artificial insemination by Pope Pius XII in 1949 and in his subsequent references to this question and <sup>7</sup> to in vitro fertilization. The pope's ethical teaching is grounded in human reason and human nature which are by definition distinct from faith and available to all human beings.

A third characteristic of Catholic moral theology is the role of the church. In agreement with other Christian ethics, Catholic moral theology acknowledges a role for the church as a moral teacher. The distinctively unique Catholic understanding of the church recognizes a

special teaching role belonging to the hierarchical magisterium (the teaching office of popes and bishops) in the church. Of special importance for this paper is the papal teaching office. The infallible teaching office is distinguished from the authoritative, authentic non-infallible teaching office. The latter teaching office is generally exercised by the pope in encyclicals written to the bishops of the church and to all Catholics, in papal allocutions and addresses to more limited audiences and in the decrees of the Roman congregations which carry out the work of the church. Catholic theologians generally agree that on specific moral questions treated in encyclicals, and especially in the less authoritative form of papal allocutions, the authoritative, authentic noninfallible papal teaching office is usually being exercised.<sup>8</sup> A few decades ago it was widely held that if the pope goes out of his way to speak on a controverted subject it is no longer a matter of free debate among Catholic theologians.<sup>9</sup>

This understanding of the response to the papal teaching office has recently been challenged. Many Roman Catholic theologians today maintain that dissent from such noninfallible papal teaching is a possible option for Catholic theologians and faithful alike. In fact, the possibility of dissent in this case is proposed as totally in keeping with the traditional self-understanding of the Roman Catholic Church even though it was not popularly recognized.<sup>10</sup> Whether or not dissent is allowed on specific issues depends on the particular case, and here there is much discussion. Recall the controversies within the Roman Catholic Church about artificial contraception for married couples. In my judgment the Catholic moral theologian must always acknowledge the unique hierarchical teaching office and respect its teaching, but at times



can and even should dissent from its teaching.

The discipline of moral theology must give attention to these three aspects which might even be called sources of moral theology--faith, reason and the teaching of the church. Moral theology is a discipline with a long history so that anyone who is working in this discipline must be familiar with that historical development but at the same time be in constant dialogue with those other religious ethics with which so much is shared and also with contemporary philosophical and scientific thought.

The body of this paper will now examine the question of in vitro fertilization and embryo transfer from the perspective of Roman Catholic moral theology.<sup>11</sup> The first section addresses ethical questions and issues which have been discussed previously but which are also connected with the ethical evaluation of this new reproductive technology. The second section will consider the specific question of in vitro fertilization and embryo transfer.

#### Ethical Issues Previously Discussed

This section will discuss questions that have existed apart from the specific topic of this paper but which are also involved in evaluating embryo culture and transfer. The following major issues will be identified and treated: anthropological presuppositions; obtaining sperm and oocytes; the meaning of human parenthood; the beginning of truly human life.

Anthropological presuppositions. Anthropological presuppositions can be reduced to the attitudes toward human existence, progress in human history and technology. All who discuss specific ethical questions have such attitudes and presuppositions even if they are not explicitly articu-

lated. These attitudes may be derived from a faith vision or they may be grounded in other sources. For the moral theologian these attitudes are greatly influenced by a faith perspective. There can be optimistic or pessimistic views of human persons; progressive or despairing views of human progress in history, positive and negative attitudes to technology.

My theological perspective or horizon views human existence in terms of the fivefold Christian mysteries of creation, sin, incarnation, redemption and resurrection-destiny. Obviously such a horizon eliminates onesided approaches to these questions. Human beings are created good, share even now in the power of the risen Lord, and look forward to the fullness of eternal life. However, human finitude will always exist; sin still affects the hearts of human beings and the structures of social existence and the future of the fullness of life always lies beyond us. In this perspective there exists a possibility for some truly human progress despite setbacks and the ever-present threats, but any naively optimistic or progressive understanding of human progress is denied.

From a more philosophical perspective, Thomas Aquinas, the most significant Roman Catholic theologian, anticipated many moderns by basing his ethics on the human being who is an image of God precisely insofar as being endowed with intellect, free will and the power of self-determination.<sup>12</sup> However, human beings exist as corporeal persons in time and space with other human beings, and they are more than just freedom events. One practical conclusion is that freedom is not the only ethical consideration because other elements (e.g. justice) might enter into consideration. For example, some human experimentations will be morally

wrong even though all the parties involved freely consent to them.

Technology will always be at the service of the human, but the human includes much more than just the scientific or the technological. The ecology question reminds us that technological progress and human progress are not the same. Sometimes in the name of the human it is necessary to say no to what one type of technology or one science can do.

Obtaining sperm and oocytes. The Roman Catholic papal magisterium has been opposed to artificial insemination (AIH) because masturbation cannot be used to obtain sperm. As early as 1897, the Congregation of the Holy Office decreed that artificial insemination was illicit.<sup>13</sup> In the light of previous and subsequent theological positions, the decree was interpreted to condemn artificial insemination precisely because the seed was obtained by means of masturbation. Before that decree was issued two moral theologians (Palmieri and Berardi) indicated that perhaps masturbation in the case of artificial insemination would not be wrong because the seminal ejaculation was directed to the fecundation of the ovum. After the decree of 1897, both authors retracted their position.

In 1919, Arthur Vermeersch proposed that artificial insemination is not morally wrong if the semen is not obtained by means of masturbation. He suggested the puncturing of the epididymus or anal friction or massage. Many Catholic theologians writing before 1949 agreed with this position thereby indicating that the reason for the condemnation of artificial insemination in 1897 was due to the fact that the semen was obtained through masturbation.<sup>14</sup> Masturbation as a means of obtaining semen for curing infertility or for seminal analysis was condemned by the Holy Office in 1929<sup>15</sup> and again by Pope Pius XII in 1956.<sup>16</sup> In 1949 in his first address on artificial insemination, Pope Pius XII also condemned masturbation and all acts contrary to nature as means of obtaining semen.

The official papal teaching and the theologians appeal to human reason and the natural law to justify the condemnation of masturbation as a way of obtaining semen either for artificial insemination or for seminal analysis. The sexual faculty has a twofold purpose--procreation and love union. Every sexual actuation must be an act which is open to procreation and expressive of love. The act of masturbation is always wrong because it is neither open to procreation nor expressive of love. No good end or purpose can ever justify an act which is always and everywhere wrong. One could for a sufficient reason licitly take semen from  
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the male, but not by means of sexual actuation.

Today the majority of Roman Catholic theologians writing on the subject reject such reasoning and its conclusion. Masturbation is not always and intrinsically wrong. These theologians disagree with the analysis of the older approach and with the underlying concept of intrinsically evil actions when the action is defined in terms of the physical structure of the act itself. Although there are different ways of explaining a newer approach, opponents of the older position agree that the problem is one of physicalism--identifying the human moral act with the physical structure of the act. The intentionality and purpose also codetermine the moral meaning of the act. The procuring of semen for  
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semen analysis or for AIH is judged not to be morally wrong.

Such discussions also remind us that the obtaining of sperm and oocytes can involve ethical issues. Today there are risks taken by the would-be mother involved in hormonal treatments to induce superovulation, in the process of removing oocytes by laparoscopy and in transferring the embryo and in further monitoring. From an ethical perspective these



risks are comparatively slight and can be justified by other values and reasons.

Nature of human parenthood. In vitro fertilization involves a new process of human parenthood which raises the question about what is ethically normative in terms of human parenthood. Various aspects of the question have been considered in connection with artificial insemination with the husband's seed and also with donor's seed. In vitro fertilization now allows for fertilization to occur outside the woman and offers the opportunity for women with problems such as occluded fallopian tubes to conceive in an artificial way and have a child of their own.

The first consideration will involve artificial insemination with the husband's sperm (AIH). In this case the so-called natural process of the ejaculation of male seed in the vagina of the female does not take place, but the husband's seed is artificially inseminated. The morality of this procedure (as distinct from the question of how the semen is obtained) was frequently discussed by Catholic moral theologians in the twentieth century. The opinion affirming the moral acceptance of AIH, provided the sperm was obtained without sexual actuation, was proposed<sup>19</sup> by Arthur Vermeersch and then explained by Gerald Kelly. Husband and wife have a right to propagate by any means which is not in itself evil. Just as every human being has a natural right to preserve one's life and can use artificial means to do so when the normal means are not helpful or available; so the married couple, when unable to generate by the normal means of marital intercourse, may use artificial means provided they are not sinful. The assumption in such reasoning is that artificial in-

semination itself is not a sinful means. Theologians were quite divided  
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on this issue.

This debate among Roman Catholic theologians came to an end after Pope Pius XII's address to the Fourth International Congress of Catholic Doctors on September 29, 1949. The pertinent part of the papal allocution follows:

Although one may not a priori exclude new methods for the sole reason that they are new; nevertheless, as regards artificial insemination, there is not only reason for extreme reserve, but it must be entirely rejected. To say this is not necessarily to proscribe the use of certain artificial means designed only to facilitate the natural act or to enable that act, performed in a normal manner, to attain its end.

We must never forget this: It is only the procreation of new life according to the will and plan of the Creator which brings with it--to an astonishing degree of perfection--the realisation of the desired ends. This is, at the same time, in harmony with the dignity of the marriage partners, with their bodily and spiritual nature, and with the normal and happy development of the child.<sup>21</sup>

In 1951 Pius XII again broached this topic and clarified in greater detail the meaning of the marital act:

In its natural structure the conjugal act is a personal action, a simultaneous and immediate cooperation on the part of the husband and wife which by the very nature of the agents and the propriety of the act is the expression of the mutual gift which according to Holy Scripture brings about union 'in one flesh only.' There is something much more than the union of two germ cells which may be brought about even artificially, without the natural action of husband and wife. The conjugal act ordained and willed by nature is a personal act of cooperation, the right to which husband and wife give each other when they marry.<sup>22</sup>

Moral theologians then attempted to state systematically and coherently the Catholic position on the nature of the marital act in the light of generally accepted theories and of these addresses of Pius XII. Sexual actuation which is in accord with the plan of God must be both open to

procreation and expressive of love union. This is the nature of the sexual actuation which human beings must always observe. According to Ford and Kelly (recall that Kelly himself had previously favored AIH):

For Pius XII seems to be saying that just as it is wrong to violate the natural design by excluding the basic procreativity of the act from the conjugal embrace (by contraception), so also it is wrong to violate the natural design by excluding the conjugal embrace, that is, the personal self-donation of the partners, from the procreative activity (by artificial insemination). Artificial insemination is condemned precisely because it separates procreation from the personal act of loving self-surrender. In other words the marriage act has a natural design as an act of conjugal love too.<sup>23</sup>

Often the official hierarchical teaching in the Roman Catholic Church has not been properly understood especially in terms of its condemnation of artificial contraception. The official teaching is not pronatalist at any cost, as the condemnation of AIH testifies. The ultimate reason for the condemnation of both contraception and of AIH rests on an analysis of the sexual act itself. Sexuality has a twofold purpose--procreation and love union. Every sexual actuation must be both open to procreation and expressive of love. This analysis of the act and its God-given design provides the basis for the condemnation of artificial contraception and of AIH (as well as of masturbation). Logically, those who disagree with the official hierarchical teaching on contraception should also disagree with the condemnation of AIH, for both condemnations rest on the same act analysis. As a matter of fact many Roman Catholic theologians today do not accept this analysis of the physical act and are in favor of contraception and AIH when there are sufficient reasons. To my knowledge, no contemporary Catholic theologian who has accepted artificial contraception has condemned AIH.

Sexual actuation does not always and everywhere by its very nature have to be both open to procreation and expressive of love union. Love union

and procreation are united not in the act but rather in the marriage relationship and in the partners. Consequently, with many other Catholic theologians I accept the morality of AIH.<sup>24</sup> In the contemporary literature outside Catholic moral theology it seems there have been no major attempts to prove that AIH is wrong.

In his address of September 29, 1949, Pope Pius XII condemned AID both outside and within marriage. The fundamental reason excluding AID is that the procreation of new life must be the fruit of the marriage and of the marriage partners. This is the primary reason against AID proposed by most Catholic theologians and by many others. Pope Pius XII phrased the objection primarily in terms of the rights of the spouses who alone have an exclusive, nontransferable and inalienable right over their bodies for the purpose of generating new life.<sup>25</sup>

Those who reject AIH maintain that the act of sexual intercourse must be both open to procreation and expressive of love. Those opposed to AID argue that procreation and love union must always be united in the two persons who covenant their lives to one another in marriage. The child must be the fruit of their love and the fruit of their bodies. The inability of one of the partners to generate offspring is part of the "worse" of the marriage promises which the couple make to one another. The two have made a covenant to share their love and their life. To bring in an oocyte or a sperm from outside the covenant relationship violates the very meaning of this relationship.

Other arguments proposed against AID are based on the consequences that might come from such a procedure. AID might harm the future psychic development of the child-to-be. AID could cause psychic difficulties for the male who is unable to have a child of his own and could thereby threaten



even the marriage itself. In addition other undesirable consequences are the buying and selling of sperm and the depersonalization of the procreation of offspring.

In general, I give great weight to the argument from the meaning of the marriage covenant and from the fact that the child is the fruit of the love and the bodies of husband and wife. However, I do not believe that these reasons constitute an absolute prohibition against AID. There are strong reasons to counsel against an easy acceptance of AID. Likewise, the other reasons proposed against it deserve serious consideration and are factors that cannot be readily passed over. In my judgment, adoption is to be preferred. However, I cannot exclude the possibility that AID could be a morally good choice in some circumstances despite serious problems that are present. Ways could be developed of preventing some possible abuses. It would not be necessary to buy and sell sperm. In one clinic in France, the sperm is freely donated by a married man who together with his wife consents to do this. In this way a personal aspect is maintained and any grossness involved in selling sperm is avoided.<sup>26</sup>

In general, it should be pointed out that the majority of Roman Catholic theologians condemn AID as morally wrong. Many who morally accept AIH do not allow AID.<sup>27</sup> Karl Rahner, who allows experimentation on in vitro fertilization, does not accept AID.<sup>28</sup> Debate also continues<sup>29</sup> among other Christian ethicists and philosophers.

AID outside marriage presents a different perspective especially in the light of the Judaeo-Christian tradition which has traditionally seen childbearing and rearing within the context of marriage. For this

reason and all that lies behind it AID outside marriage is morally unacceptable. Further questions involving procreation and the meaning of parenthood will be discussed in later sections.

The beginning of human life. The beginning of truly human life looms large in any discussion of in vitro fertilization and embryo transfer. What is it that is present in the preimplantation embryo? In these discussions I avoid the term person and speak of truly human life as that life which deserves the same value, rights and protection due the human person as such.

In the context of the debate over abortion, there have been many articles and books written on the question of the beginning of truly human life and the criteria or methodological approaches to be employed in determining when truly human life begins. The papal and hierarchical magisterium of the Roman Catholic Church have shown complete unanimity even in recent years in maintaining that from the moment of conception the fetus is to be treated as truly human life. However, the hierarchical magisterium still recognizes that theoretical doubt about the beginning of human life can exist, but in practice one must act as if <sup>30</sup> truly human life is present from the moment of conception.

In the contemporary ethical writing on this topic, I discern four <sup>31</sup> different types of criteria for deciding when truly human life begins. The individual-biological criterion judges the existence of truly human life in terms of some physical, biological or genetic aspect of the individual being. A relational criterion maintains that truly human life begins once there is an established human relationship between parents and fetus. A multiple criterion approach includes biological, psychological and cultural factors with a developing value attached to the fetus

until all these aspects are more present. A conferred rights criterion recognizes difficulties with the metaphysical basis of the other proposals and affirms that rights are conferred by those people who contract to make up the society.

In evaluating these criteria and/or conclusions, I begin with the presupposition that almost all would accept that infanticide is wrong. As a result, one must propose a criterion for the beginning of truly human life which can never be used to justify infanticide.

I reject the conferred rights approach because it does not go to the heart of the matter. Why should rights be conferred on the fetus in the first place? In addition, my philosophy of rights sees these as inalienable rights of the human being and not something conferred by others. The relational criterion if it is to be based on human relations as constituting the beginning of truly human life would not be present until well after birth. Human relations involve some type of reciprocity. A multiple approach stresses the need for psychological and cultural factors as well as biological, but in my judgment there is much more psychological and cultural development which takes place after birth than takes place before birth. I employ the individual-biological criterion. In a sense this is the same general criterion used in our determination of human death. Whether the test for death be cessation of heartbeat, of breathing or of electrical brain activity, these are all criteria of the individual-biological order.

Within this criterion I maintain that truly human life should be judged to be present two to three weeks after conception. My position recognizes that potentiality is present very early and much development

occurs on the basis of what has been present from the very beginning. Later points of development are ruled out as constituting no more than developing stages and not crucial qualitative differences that are so significant as to determine the beginning of truly human life. Many who adopt this criterion choose the moment of fertilization or conception as the beginning of truly human life. From the first moment of conception there is a unique never-to-be-repeated genotype.

My position rests heavily on the concept of individuality. Individuality is not really present at the very beginning because twinning and recombination remain possible. Only after about three weeks is this individuality present. These arguments are buttressed by two other considerations--before this time the cells are pluripotential and cannot change without the appearance of the primary organizer which is not yet present. Also the many fertilized ova which, even in the normal process of reproduction, are spontaneously aborted before implanting in the uterus also tend to argue that we are not dealing here with truly human life. Although my position maintains that truly human life is not present until two to three weeks after conception, before this time the zygote, morula and blastocyst do have some value and importance.

#### Clinical In Vitro Fertilization and Embryo Transfer

All the questions considered thus far are related to the ethical decisions about in vitro fertilization and embryo transplant. Those who oppose obtaining the semen by masturbation or oppose AIH or believe that human life is present from the very moment of conception would logically be opposed to in vitro fertilization and embryo transfer under any circumstances. One should not be surprised to learn that Pope Pius XII in 1956 merely stated that experiments in artificial human fecundation in



vitro must be rejected as immoral and absolutely illicit. However, from the positions I have taken on the issues up to now, logically the question of in vitro fertilization and embryo transplant remains open. This section will now consider the ethical issues dealing specifically with our topic.

Discards and Failures. In practice many fertilizations are usually done but only one embryo is ultimately transferred. The remaining fertilized ova are then discarded. In the process of trying to implant the embryo there will also be many failures. What about the problem of these discards and failures? According to my position they do not constitute truly human life, but obviously these early embryos do have a value and importance. However, since they are not deserving of the protection of truly human life, some discards and failures cannot constitute an absolute condemnation of in vitro fertilization and embryo transplant. It could be judged that their loss is compensated for by the good to be attained if the in vitro fertilization and embryo transplant becomes successful. In this connection it is necessary to recall that even in the normal process of reproduction many fertilized ova do not implant and are lost. Despite a few contrary voices, the vast majority of authors recognize that a large proportion of fertilized ova are

never implanted. Means should be taken to insure that discards and losses are not excessive.

Risks to the child-to-be. What right do those generating new life have to expose the child-to-be to risks such as future abnormalities? Here again it is necessary to recall that there are risks for the child-to-be in the normal process of reproduction.

For many ethicists and scientists, such as R. Edwards, there

is no real problem here. The fetus after implantation can be monitored by all types of prenatal diagnosis such as ultrasonics and amniocentesis. If any abnormalities appear, the fetus can be aborted. Edwards concludes that the risks of abnormal offspring following embryo transfer would then  
 36  
 be very small.

However, from my perspective I cannot accept the general solution of abortion of deformed fetuses, since a truly human life is already present. My ethical analysis must then deal somewhat differently with the question of the risks to the child-to-be.

Can any reason justify exposing the child-to-be to some risk? The potential conflict exists between the desire of the parents (supposing now the case of a married couple) to have a child and the risks to the child-to-be. Do the parents have a right to have a child? In general for all people one would have to deny that there is an absolute right to have a child. Catholic theology and discipline respond by saying that a married couple has a right to place that act (the marital act) which is apt for generation, but whether or not generation follows is beyond their control and their right. Nor can one say that parents have a right to do everything possible to have a child, for there are obvious limits.

However, the desire for a married couple to have a child is something intimately connected with the reality of their marriage. The Christian tradition recognizes that one of the goods of marriage involves offspring. There is a strong connection between children and marriage. The desire of a married couple to have a child is much different from the desire of a nonmarried person to have a child. In this context there can

be justification in exposing the child-to-be to some risks. Even in normal reproduction there are such risks. I would conclude that the risks in in vitro fertilization and embryo transfer should be about the same as in the normal process. Unless this type of assurance can be given, the artificial procedures would be wrong because of the disproportionate danger of risk to the child-to-be. At the very minimum, experimentation on lower animals must be done to such a degree as to give assurance that the risk to the child-to-be is proportionate--that is, about the same as in the normal process.

The nature of human parenthood. Does in vitro fertilization de-personalize marriage and parenthood? The origin of the child is separated from the sphere of the specifically marital (bodily, sexual) love. The child can undoubtedly be the result of a loving decision on the part of the parents but the bodily aspect is missing. Aspects of this question have already been discussed in considering AIH and AID.

Some, echoing the fear of Pope Pius XII that the domestic hearth<sup>37</sup> will be turned into a biological laboratory, claim that the laboratory<sup>38</sup> reproduction of human beings is no longer human reproduction. Undoubtedly there are certain human values in the normal way of parenthood and reproduction. However, in vitro fertilization and embryo transfer are proposed only for that limited number of situations in which the normal process cannot take place. On the other hand, I object to the approach of Joseph Fletcher who seems to prefer the control of technology to the<sup>39</sup> genetic lottery of chance.

Needs and priorities. In vitro fertilization and embryo transfer is now proposed as a remedy for infertile parents when the wife has oc-

cluded oviducts and therefore is unable to have a child. The problem of infertility due to occluded ducts might affect two per cent of the female population. However, some of these people can be helped by reconstruction of the oviduct. In vitro fertilization and embryo transfer could be of great benefit to a very small percentage of parents who are unable to have a child of their own. In addition, this technique could be used for many other purposes. A woman who lacks oocytes of her own could have an embryo formed from her husband's sperm and a donor's ovum transferred into her body. A woman unable to support a pregnancy could use a surrogate mother.

The question of priorities within medicine and science is intimately connected with the narrower question of the need for in vitro fertilization and embryo transfer. The danger constantly lurks of giving so much attention to comparatively esoteric procedures that basic medical care (e.g., maternal and prenatal health care) tends to be neglected. In general, many today agree that more emphasis should be put on preventive health care and not as much on crisis intervention. However, on the other hand the costs involved in in vitro fertilization and embryo transfer do not amount to that much compared to other more esoteric medical technologies.

The wedge argument. One very important aspect which arises in both everyday conversation and in the more reflective literature can be summarized in what is often called the principle of the wedge or the slippery slope or the camel's nose in the tent argument. If we allow a, then we open the door to x, y and z. As generally understood this argument does not presuppose an absolute and logically necessary connection



between the first step and the second (i.e., if you give someone an inch, they cannot logically claim a right to a mile). However, there is a tendency to move in this direction. Perhaps many of the arguments advanced for a could also be advanced for x, y and z even though a logically differs from x, y and z. The wedge argument must be analyzed and applied very carefully.<sup>41</sup> On the one hand, the wedge can be readily employed to justify the status quo; while, on the other hand, history often shows there was more of a connection between the first step and the final outcome than had been anticipated. There are many different aspects of this problem involving possible abuses which deserve some discussion.

Now that the technology of in vitro fertilization and embryo transfer has been successfully accomplished at least once, this technique could be used for many different purposes and reasons. These new technologies could be used as a way of improving the gene pool of the human race and making better people. Here it is important to recognize the distinction between positive and negative eugenics. For many reasons I am totally opposed to any type of positive eugenics. This new technology should be confined to helping people with infertility problems. In this way it is possible to construct what might be called a firebreak thereby preventing the gradually escalating uses of this technology to the point of great abuses.

At the present time requests are generally limited to do research on in vitro fertilization and preimplantation embryos. Once this research has been done and the technologies relatively perfected there

will be demands and requests to do research on the embryo after the time of implantation. Science is rightly striving for knowledge and truth, since such striving constitutes the very goal and lifeblood of scientific inquiry.

In theory one must firmly acknowledge that there are limits to the pursuit of truth. There are some things in sociology that we might never be able to learn because the only way to discover such truths might violate the right to privacy of certain individuals. Medical science itself recognizes some limits; for example, we could learn much more if we allowed medical experimentation on living human beings in the same way we experiment on animals.

From my ethical perspective truly human life is present two to three weeks after conception or shortly after the implantation of the embryo. Hence experimentation after that time and attempts to culture embryos in vitro beyond this stage of development raise insurmountable ethical problems. I am fearful that such a step will come about and want to prevent it.

An important consideration must be the effect of the new reproductive technologies on the family. The family occupies a unique and very significant place and role in society. The bearing and rearing of children ordinarily take place within the family context. In the last few decades we have recognized many problems and changes involving the family in contemporary society. Single parent families have become more and more common and generally acceptable both in theory and in practice.

There is a legitimate concern that these new technologies might affect the family deleteriously. This can readily be avoided by limiting

in vitro fertilization and embryo transfer to those who are truly involved in a family situation involving a heterosexual couple in an established relationship. In this way added pressures will not be put on the family if these techniques are so limited.

Another problem concerns the very meaning of medicine and its purposes. Medicine, according to Paul Ramsey, exists to cure the medical ills of people but should not be used for nonmedical purposes or to fulfill people's wishes or desires.<sup>42</sup> Such reasoning involves serious flaws, but there is also an element of truth that cannot be ignored. In our everyday life even now we accept the fact that medicine deals with nonmedical problems and is not always used for strictly medical purposes. Cosmetic surgery constitutes one obvious example. This practical example finds theoretical grounding in an understanding of medicine as being at the service of the whole human person and not merely limited to the narrower range of the strictly medical aspects of the person.

On the other hand, there would be obvious abuses if medical technology can be used to fulfill one's wishes and desires with no further qualification. It is necessary to look more deeply into the question of the wishes and desires for a child. As mentioned above, not even married couples possess a right to have a child. However, a strong connection exists between marriage and children which distinguishes the desire of the married couple for a child from the desire of others. All admit that a married couple can use such means as fertility testing, fertility treatment and arranging coitus at the proper time to help achieve their desire for a child. Most ethicists acknowledge that arti-

ficial insemination (for many, including myself at times, AID) is morally acceptable. The acceptance of in vitro fertilization and embryo transfer for married couples would not open the door to the danger that wishes and desires alone justify any medical treatment or intervention.

Another very significant danger involves our attitude toward the control of our offspring and our lives as well as our compassion and concern for the abnormal, the retarded and all those who fall below the accepted standards of normality. In general we must be open to all legitimate attempts to overcome disease, abnormality and suffering; but we must also recognize that in the end it will be impossible to exercise perfect control over our human existence. An unbalanced quest for the goal of perfect control would have deleterious effects on our compassion for those who are suffering which has traditionally been called a hallmark of Judaeo-Christian civilization. Newer discoveries such as reproductive technologies do not necessarily involve a lessened compassion and concern for the abnormal, but we must be ever vigilant in this matter.

There already exists a popularly accepted slogan that every child should be a wanted child. In many ways I agree with the sentiments behind such an adage, but I would have great difficulty in accepting the possibly broader indications that we can control everything about our offspring and our own lives. Experience reminds us there are many things that happen to us in life that we do not want. The reality and mystery of suffering will always accompany us in our living and in our dying. Human existence would be rather sterile if we were able to totally determine everything that happens to us.



Two other issues. The thrust of the argument proposed thus far, especially in view of the danger of excesses and abuses, has limited in vitro fertilization and embryo transfer to married couples. Now the question is explicitly raised about such reproductive technologies using donor sperm and/or donor oocytes. This procedure involves an extended form of AID with the possibility of a donor ovum as well as a donor sperm. From an ethical perspective I have already proposed that AID could sometimes be justified although there are many ethically problematic issues involved. On the ethical level, I am hesitant about the morality of embryo culture and transfer involving donor gametes. On the level of public policy at the present time I do not approve of in vitro fertilization and embryo transfer in these cases. There are many serious moral questions (not serious enough to constitute an absolute moral prohibition) involved in AID which are not present in AIH. As a matter of public policy it would be very difficult to monitor all these very significant problems. In addition, there are still many legal questions about AID, so one should proceed rather cautiously in this area. In introducing new procedures involving the danger of abuses, prudence seems to indicate a cautious approach.

Another question concerns a surrogate mother for those women who are unable or unwilling to carry their own children. Here again there is a slippery slope from being medically unable to being unwilling whether for very serious or for frivolous reasons. There are serious reservations about such a procedure precisely because of the bodily relationship existing between the woman who carries the child and the child. In addition, there could also be complicated and perplexing

legal problems. By preventing such a procedure one also places a firm firebreak in the path of possibly spreading abuses of this new reproductive technology.

Ethical conclusions. In conclusion my analysis of the morality of in vitro fertilization and embryo transfer accepts such a procedure under the following conditions:

1. Discards and losses are minimized as much as possible.
2. There must be a proven assurance that the danger of harm to the child-to-be is about the same as in normal conception. A thorough investigation of all the available scientific data must be made to see if this condition exists at the present time.
3. The procedure is limited to an established heterosexual couple whose own sperm and ovum are fertilized in vitro and then transferred into the womb of the wife.

The discussion has generally been in terms of the clinical work done with individual patients. What about basic research in in vitro fertilization and transfer of preimplantation embryos? Almost all of the relevant issues have been discussed previously. In addition, the canon of informed consent with regard to experimentation is definitely called for in this case. Research can be done at the human level only after thorough research has been done on lower levels. The purpose of the research must be specifically stated and the need for such research must be demonstrated. The nature of the matter involved in the research calls for respect and economy avoiding unnecessary waste. The research should be restricted to preimplantation embryos and any attempts to culture the fetus beyond this stage are wrong.

Legality and public funding. This paper has addressed the question of in vitro fertilization and embryo transfer from an ethical perspective. What about public policy and public funding? There are three distinct issues involved here--morality, legality and public funding. Is my position on morality too liberal or too restrictive in terms of legality and public funding?

Some might argue that my position is too liberal in the light of the many people in our society who are opposed to such a technique. Some of them might be opposed because they believe truly human life is involved. Even in the light of my ethical position, one could still conclude against the legality or especially against the public funding of such research and techniques. I would not make such judgments.

Is the ethical position taken here too restrictive for a public policy of acceptance and funding? There are many people who might object to the restrictions proposed in this paper--clinical work restricted to the ovum and sperm of husband and wife with the embryo transferred into the uterus of the wife; no surrogate mothers; no culturing of or experimentation with postimplantation fetuses.

Many reasons of a prudential nature support the position outlined above. In dealing with new technologies which have a great impact on life and society caution is in order. Many ethical theories give some if not all importance to consequences, but no one possesses the Solomonic wisdom to know what will be the consequences of these new technologies. It will be important to see what consequences occur from a somewhat restrictive approach before entertaining other possibilities.

An objection might be raised that I am unfairly thrusting my moral positions, especially on the question of the beginning of human life, on

others and preventing them from acting in accord with a different understanding. There are a number of possible responses to such an objection. Some could reach the same conclusion on different grounds such as the prudential reasons mentioned above. Others could conclude that there are many people who are deeply convinced that truly human life is present after implantation and public peace calls for respect for this position especially when there are no overwhelming rights in collision with this understanding. Others could arrive at this same conclusion not on the basis that truly human life is present in the postimplantation fetus, but on the basis that the fetus at that time in development has greater value than the reasons proposed for extending the culturing of embryos beyond this time.

There are significant differences between the law on abortion and policy on the legality and funding of research. Although I believe in a comparatively early time for the beginning of truly human life, I have accepted the Supreme Court's ruling on abortion law and opposed efforts to overturn this ruling through a constitutional amendment. In abortion the rights of the mother are involved. In our pluralistic society in which there is dispute about the beginning of human life I can understand a conclusion which says that the benefit of the doubt should be given to the rights of the mother and her freedom to act. However, in this case there is no conflict between the fetus and the rights of the mother or any strict human rights.

In conclusion this paper maintains that under certain conditions in vitro fertilization and embryo transfer are morally acceptable and also proposes this conclusion as a basis for public policy and funding.



1

The characteristic Roman Catholic emphasis on human nature and human reason in ethics is universally recognized. From a Protestant perspective, see Roger Mehl, Catholic Ethics and Protestant Ethics (Philadelphia: Westminster Press, 1971) and especially James M. Gustafson, Protestant and Roman Catholic Ethics: Prospects for Rapprochement (Chicago: University of Chicago Press, 1978).

2

E.g., Gerald Kelly, Medico-Moral Problems (St. Louis: The Catholic Hospital Association, 1958). For a recent exception which bases its approach to in vitro fertilization on the Christian content of the faith instinct, see Donald J. Keefe, "Biblical Symbolism and the Morality of in vitro Fertilization," Theology Digest 22 (1974), 308-323.

3

Josef Fuchs, Esiste una morale cristiana? (Rome: Herder, 1970). For a summary of this debate and a conclusion agreeing with mine, see Richard A. McCormick, "Notes on Moral Theology," Theological Studies 32 (1971), 71-78; 34 (1973), 58-61.

4

Paul Ramsey, Fabricated Man: The Ethics of Genetic Control (New Haven: Yale University Press, 1970).

5

Harvey Cox, On Not Leaving It to the Snake (New York: Macmillan, 1967). In later writings Cox has modified his understanding of anthropology and of eschatology.

6

Joseph Fletcher, "New Beginnings in Life: A Theologian's Response," in The New Genetics and the Future of Man, ed. Michael Hamilton (Grand Rapids, Michigan: William B. Eerdmans Publishing Co., 1971), pp. 78-89; Joseph Fletcher, The Ethics of Genetic Control (Garden City, New York: Anchor Press/Doubleday, 1974).

7

Pope Pius XII, "Allocution to the Fourth International Congress of Catholic Doctors," September 29, 1949; English translation: The Human Body: Papal Teachings, selected and arranged by the monks of Solesmes (Boston: St. Paul Editions, 1960), pp. 114-119. Artificial insemination was referred to in the following subsequent papal addresses of Pope Pius XII: "Allocution to Italian Midwives," October 29, 1951; English translation: The Human Body, pp. 149-178; "Allocution to the Second World Congress on Fertility and Sterility," May 19, 1956; English translation: The Human Body, pp. 384-394; "Allocution to the Seventh International Hematological Congress," September 12, 1958; English translation: The Pope Speaks 6 (1959-60), pp. 392-400. The official versions of these and other papal documents are found in Acta Apostolicae Sedis.

8

For example, the vast majority of Catholic theologians believe that the papal condemnation of artificial contraception does not constitute an infallible teaching. A few view this teaching as infallible not on the basis of inclusion in encyclicals but because it has been constantly taught as such by the pope in union with the bishops throughout the world.

9

Franciscus X. Hürth, "Annotationes," Periodica de Re Morali Canonica Liturgica 41 (1952), 245-249.

10

Joseph A. Komonchak, "Ordinary Papal Magisterium and Religious Assent," in Contraception: Authority and Dissent, ed. Charles E. Curran (New York: Herder and Herder, 1969), pp. 101-126.

11

For a concise summary of the significant issues involved, see André E. Hllegers and Richard A. McCormick, "Unanswered Questions on Test Tube Life," America 139 (August 19, 1978), 74-78.

12

Thomas Aquinas, Summa Theologiae, I<sup>a</sup>-II<sup>ae</sup>, Prologue.

13

Enchiridion Symbolorum Definitionum et Declarationum de Rebus Fidei et Morum, ed. H. Denzinger, A. Schönmetzer, 32nd ed. (Herder: Barcelona, 1963), n. 3323. Hereafter cited as D.S.

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The historical development of the teaching on artificial insemination has been traced in a number of different places. See William Kevin Grover, Artificial Insemination among Human Beings (Washington: The Catholic University of America Press, 1948); Hyacinthus M. Hering, De Fecundatione Artificiali (Rome: Officium Libri Catholici, 1952).

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D.S., n. 3684.

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Human Body, pp. 390-392.

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Thomas J. O'Donnell, Medicine and Christian Morality (New York: Alba House, 1976), pp. 257-267. As O'Donnell points out, the older teaching was reaffirmed by the bishops of the United States in Directive 21 of The Ethical and Religious Directives for Catholic Health Facilities issued in November 1971.

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E.g., Bernard Häring, Medical Ethics (Notre Dame, Indiana: Fides Publishers, 1973), pp. 92-93.

19

Arthur Vermeersch, De Castitate et vitiis oppositis (Rome: Universita Gregoriana, 1919), n. 241; Gerald Kelly, "The Morality of Artificial Insemination," American Ecclesiastical Review 101 (1939), 109-118.

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For aspects of this debate, see The Clergy Review 23 (1943), 564; 25 (1945), 268-270, 335-336, 381-382; 29 (1948), 359-360; 30 (1948), 144, 357-358; also Theological Studies 8 (1947), 106-110; 10 (1949), 113-114.

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Human Body, p. 119. This translation is from Kelly, Medico-Moral Problems, pp. 229-230.

22

Human Body, pp. 171-172. This translation is from the official N.C.W.C. translation.

23

John C. Ford and Gerald Kelly, Contemporary Moral Theology II: Marriage Questions (Westminster, Maryland: Newman Press, 1963), pp. 289-290.

24

E.g., Rodger van Allen, "Artificial Insemination (AIH): A Contemporary Re-Analysis," Homiletic and Pastoral Review 70 (1969-1970), 363-372; Richard A. McCormick, "Notes on Moral Theology," Theological Studies 32 (1971), 94-97; Roger Troisfontaines, "L'insémination artificielle: Problèmes éthiques," Nouvelle revue théologique 95 (1973), 764-778; Bernard Häring, Ethics of Manipulation: Issues in Medicine, Behavior Control and Genetics (New York: Seabury Press, 1975), pp. 194-198; John F. Dedek, Contemporary Medical Ethics (New York: Sheed and Ward, 1975), pp. 92-105.

25

Human Body, p. 118.

26

For the description of such a clinic and an ethical position similar to my own, see René Simon, "Expérimentations et déplacements éthiques: A propos de l'insémination artificielle," Recherches de sciences religieuses 62 (1974), 515-539.

27

For example, McCormick, Häring and Dedek have expressed such rejections of AID.

28

Karl Rahner, "The Problem of Genetic Manipulation," in Theological Investigations XI: Writings of 1965-67, I (New York: Herder and Herder, 1972), pp. 225-252.

29

James B. Nelson, Human Medicine: Ethical Perspectives on New Medical Issues (Minneapolis: Augsburg Publishing House, 1973), pp. 59-78; Law and Ethics of AID and Embryo Transfer, ed. G.E.W. Wolstenholme and D. Fitzsimons, (Amsterdam: North-Holland Publishing Co., 1973).

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Philippe Delhaye, "Le magistère catholique et l'avortement," Esprit et vie 83 (1973), 434-436; 449-457.

31

I am summarizing here material presented in my article "Abortion: Contemporary Debate in Philosophical and Religious Ethics," to be published in Encyclopedia of Bioethics (New York: Free Press-Macmillan, 1978).

32

For a similar position, see Gabriel Pastrana, "Personhood and the Beginning of Human Life," The Thomist 41(1977), 247-294.

33

Human Body, p. 389.

34

Thomas W. Hilgers, "Human Reproduction: Three Issues," Theological Studies 38 (1977), pp. 147-149.

35

E.g., C.J. Roberts and C.R. Lowe, "Where Have All the Conceptions Gone?" The Lancet No. 7905, March 1, 1975, 498-499.

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R.G. Edwards, "Fertilization of Human Eggs in vitro: Morals, Ethics and the Law," The Quarterly Review of Biology 49 (1974), 9.

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Human Body, p. 171.

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Ramsey, Fabricated Man, pp. 102-160; Ramsey, "Shall We 'Reproduce'?" II: Rejoinders and Future Forecast," Journal of the American Medical Association 120 (June 12, 1972), 1481-1483; Leon Kass, "Making Babies--The New Biology and the 'Old' Morality," The Public Interest No. 26 (Winter, 1972), 48-50.

39

Ethics of Genetic Control, p. 36.

40

Edwards, p. 10.



41

For a discussion of the wedge argument, see Sissela Bok, "The Leading Edge of the Wedge," The Hastings Center Report 1, No. 3 (December 1971), 9-11; Paul Ramsey, "The Wedge: Not So Simple," The Hastings Center Report 1, No. 3 (December 1971), 11-12.

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"Shall We Reproduce?" p. 1481.



THEOLOGICAL REFLECTIONS ON IN VITRO FERTILIZATION

Stanley Hauerwas, Ph.D.





## Theological Reflections on In Vitro Fertilization

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### 1. Theology, Ethics, and In Vitro Fertilization

It is customary for anyone testifying before such committees to establish their credentials. I have been asked to testify because I am a Protestant, a theologian, and an ethicists. I am not sure which of these is the more important nor am I sure how I can show I am competent at any of them since we live at a time when such titles are remarkably ambiguous. In vitro fertilization surely is a symbol of what a strange world in which we live, but Dr. McCarthy must have at least thought it was a little, though perhaps not equally, strange to find himself calling the University of Notre Dame to get a Protestant theologian ethicist.

Therefore even though I am here as a Protestant it is important that I make clear that I cannot pretend to speak for any identifiable religious body or any broad consensus of religious belief. What you see before you is a Methodist of doubtful theological background (when you are a Methodist it goes without saying you have a doubtful theological background); that teaches, worships, and is sustained morally and financially by Roman Catholics; who believes that the most nearly faithful form of Christian convictions is best exemplified by the often-ignored people called anabaptist or Mennonites. Obviously I can speak only for myself.

Having said this, however, does not mean I want you to take my views lightly. Humility, as it is usually understood, is not a virtue I greatly admire or embody. Even though I speak for myself I want to make clear that the perspective and arguments I will develop in this presentation I think should be the views of all

Christians. I do not presume to tell you what Christians do think about these issues, but I certainly want to tell you what they ought to think if they are to preserve their distinctive form of life.

I much appreciate that Dr. McCarthy invited me to speak from a theological perspective for that is what I intellectually care about the most. Indeed even though I have been trained as an "ethicist" and my work is usually classified as "ethics," I understand myself to be a theologian.<sup>1</sup> Yet I must warn you that for me to take seriously the task of addressing the issue of in vitro fertilization from a theological perspective will require me raise issues that you may well find irrelevant for your concern to develop principles for what should be the standards for the public policy of the nation.

For by speaking from a theological perspective I do not pretend to speak from principles that are or should be shared by everyone in our society. You should also know that my own methodological presuppositions in this respect are not widely shared among those that work in theological ethics. Rather the assumption is that theological ethics must develop arguments that should compel consent from all rational subjects irrespective of their religious convictions or lack of religious convictions. Of course, that results in the somewhat ironical state of affairs that committees such as this one invite representatives of religious communities to show how their communities' particular convictions throw light on an issue only to be told that Christian views on the subject are not necessarily related to their religious convictions. Christian ethicists therefore say what any right thinking moral philosopher or person would say.

Well I simply do not believe that. It will be the heart of my argument that theological beliefs do make a difference for how in vitro fertilization is understood. But since my own views are correlative to my theological convictions it

raises the issue of how seriously the committee can take them for consideration of public policy. Fortunately that is not my immediate problem.

It is my own view, however, that the presumed moral agreement or consensus presupposed by many philosophical and religious ethicist is unfounded. Such agreement can be maintained only by providing an account of morality so formal that it cannot possibly have any normative implications; or the implications that are claimed betray unfounded commitment to one among equally viable moral alternatives in our society. In this respect I take the moral challenge of our time to be the recognition that we live amid "fragments" of past moral positions none of which can claim our loyalty on grounds of rationality in itself.<sup>2</sup> At least by taking seriously the particularity of Christian convictions perhaps I can help clarify the difficulty of formulating public policy that involves moral issues in such a situation.

After having made this strong claim about the dependence of my argument on theological presuppositions, however, I must tell you that there is no direct connection between theological beliefs and the question of the permissibility or impermissibility of in vitro fertilization. There is nothing in scripture that says "You shall not commit in vitro fertilization." nor do I think you can show any direct connection between theological claims about God's creative and redemptive purposes and in vitro fertilization. There may be theologians who think this can be done, but I am skeptical whether they can make such arguments work.

Rather, to understand the relationship between theological claims and questions about in vitro fertilization, I must ask you to suspend presuppositions about how we usually think about religious belief and how we understand the moral life. The primary function of religious belief is not to describe the world or to determine the rightness or wrongness of particular actions, rather, it is to form a

community that understands itself as having a particular mission in the world. To be sure, that mission involves claims about the nature of the world and what one should and should not do, but those judgments are mediated by the practices established essential to being a people of a particular sort. Put starkly: for the Christian the question of the use or non-use of in vitro fertilization will be determined primarily by whether such a procedure is appropriate to our understanding of what kind of community we should be and in particular what kind of attitudes about parenting we should foster. In other words, it is not a question of whether in vitro fertilization is right or wrong, but rather it is a practical judgment of whether this kind of technique furthers or is compatible with our community's understanding of itself. Put bluntly, issues such as in vitro fertilization are fundamentally symbolic issues that are primarily determined by the wisdom of a community.

Ethically, this means that religious convictions are not usually of the sort that determine whether something is right or wrong in itself, but rather they determine what we should be. This is not the place to try to summarize the position I have been trying to develop for some time, but basically I have argued that ethics has been too concerned with "quandries" or decisions and has failed to pay sufficient attention to the notion that are as important as what we do is what we are.<sup>3</sup> Character and virtue and central moral categories as we confront the kind of issues we do because we are a particular kind of person and community. Therefore, the question of in vitro fertilization cannot be determined in isolation from the implications of its use for the character of the Christian community and individuals.

## 2. Christian Parenting and In Vitro Fertilization

By now I have probably completely frustrated you as I have yet to say anything of interest about in vitro fertilization. I am going to try to do that,



however, again I must warn you that I am not beginning by trying to answer the question, "Is in vitro fertilization right or wrong?" Kass is absolutely right to argue that the first question is not whether it is right or wrong, but what is it?<sup>4</sup> Namely, how are we to interpret or understand what it is we are involved in through the development or non-development of in vitro fertilization. My question is a bit different from his, however, as he wants to understand the procedure of in vitro fertilization and I want to begin still a step back from that question -- namely how am I to understand why it is that we feel the need to develop such a procedure at all. Is such a procedure to be understood as the result of mans' moral quest to understand himself better through science? Or is it the result of our pledge to care for one another through the office of medicine by alleviating unnecessary physical hindrances to our moral projects? Or is this procedure a mark of man's sinful pretention to insure immortality through biological continuity?

Behind these questions is the assumption the question of in vitro fertilization is first not one of decision but how to understand such a procedure in a manner that gives direction to a community's moral project. When put in this context I assume that possible misuse of the procedure is not the primary question, as every invention of man is open to perversion. The question is whether there can be a moral determination of when it should not be used.

In order to try to make this way of proceeding concrete I want to direct your attention to a childless couple who have come to their minister for counseling about their wish to have children. Now I will have to assume that this is a minister who failed to take his course in psychological counseling in seminary and therefore still thinks that Christian convictions should have something to do with how he or she talks with and even, in a moment of bravery, advises this couple. How should the minister or the couple as Christians understand the importance of having children and, in particular, their own biological children.

In other words, the question to begin with is why anyone should want to have children in the first place. We assume that such a desire is not arbitrary but based on our profoundest moral convictions. Yet it has been my experience that when you ask most people why they want or have children they become surprisingly inarticulate. They say it is fun (obviously these have never had children); that is is a manifestation of their love (but then what do you do with your children if the love fades); or it is to please the grandparents or to prevent us from being lonely (again less than good reasons, since then the child is being used for some purpose other than himself); or that children are our hope for the future (and then they always disappoint us).

I am well aware that part of the hesitantancy stems from the fact that the question seems illegitimate. And indeed I suppose it is; most of the time we simply do not have to think very much about such matters. The very institutions of culture carry expectations whose very obviousness makes such questions irrelevant. Perhaps because procedures such as in vitro fertilization are so troubling for us they are occurring exactly when our institutions do not seem to have that kind of assuredness. In doubt as to why we are having children or what we ought to do with them once we have had them, we feel more secure not raising such questions on the assumption that the unexamined life is indeed worth living. The issues raised by in vitro fertilization confront just that issue.

Presupposed in the therapeutic justification of in vitro fertilization is the assumption that biology has some extremely important role to play in parenting. That does seem obvious since biological pregnancy is the necessary condition for parenting. Beyond that obvious fact, does the demand of couples to have their own biological child suggest that in the absence of any deeper understanding of parenting our last resort is biology? No one would wish to deny the importance of the experience of pregnancy, but is it such an important experience

that we should be willing to expend huge amounts of time and money to provide that experience?

Also involved in the development of this technique is a peculiar sort of biological determinism. Often, those who defend the technique in order to give women the experience of pregnancy see nothing wrong with the further use of the technique through surrogate mothers. At once the technique is defended in the name of the crucial relation between biology and parenting and then a form of parenting is defended that is abiological.

Indeed the way critics of in vitro fertilization raise the spector of surrogate motherhood strikes me as but another indication that we are less than clear about what moral role parenting involves. For they appeal to surrogate motherhood as if it is obvious that most generally agree it is or would be a bad idea, but why should people think that? They condemn the idea one women might pay another to carry her genetic child and thus avoid the trouble and danger of pregnancy. But surrogate motherhood should not be condemned because it is open to commercial distortion or because it might involve attitudes on the part of the "non-pregnant" mother we usually feel incompatible with. the willingness to have and raise children. For it is surely possible to conceive of a women carrying another women's child out of friendship because the latter is incapable for extenuating circumstances to carry her child. Confronted with that kind of case I suspect our problem is not that we know what is wrong with surrogate motherhood, but we have no idea why we should think it right or wrong and thus become dogmatic about its "wrongness."

I mention these issues not to argue that in vitro fertilization is wrong, but only to suggest that morally it calls forward our profoundest assumptions about the role of parenting and how that role is formed by the good ends of particular communities. Because our culture is currently at a loss to give direction



to the institution of parenting, in vitro fertilization is troubling since we cannot articulate why we have developed it. For example, I suspect that the response of most people when they first think about in vitro fertilization is not "ethical" at all -- it is simply that such a technique in our culture is bizarre. We tend to think of bizarreness as an esthetic category having no ethical significance, but I think that is a mistake. For what is bizarre about in vitro fertilization is how a civilization that has approved of people aborting all unwanted children can at the same time sponsor an extraordinary technique to allow a few women to have the experience of pregnancy. Or that a civilization that has been told that we are over-populated and on the brink of ecological disaster has developed such a technique. What this indicates to me is not that we have a corrupt civilization, but that we have one that has no way of providing an understanding of what any of us are doing when we have (or don't have) children.

But we must come back to our minister counseling the childless couple. All I have tried to establish is this point is whatever the minister says to the couple necessarily will involve assumptions about why they are having children in the first place. Though it is true that Christians and non-Christians alike have children, it is not clear that morally they are doing the same thing. As I have tried to suggest, having children is not a natural fact or a necessity, but draws on our deepest assumptions about the nature of our existence.<sup>5</sup>

Therefore, for Christians, having children must be placed in the context of some very substantive claims about the nature of the world and God's relation to it. You will have to forgive me if some of what follows sounds homiletical, but there is no other way to say it. Christians believe that the world is deeply bent by sin most poignantly manifest in the distrust that characterizes all relations between people. Violence and coercion are not accidental to such a world but are integral to its nature. For example, from our perspective people are not racist because they are ignorant, but racism is but a manifestation of the fear, fueled by the corruption of the prideful assumption, that the only



way to get out of this life alone is by taking control of our existence. In other words, we believe that the forms of distrust and untruthfulness present among us are but the necessary form of the world built on the assumption that men, not God, rule.

The Christian and the Jew, believe that they have been given a special mission in such a world. Namely they have been called to form communities that manifest the trust and love possible between people when they recognize the sovereignty of God over all life. To be sure they are often unfaithful to such a task, but their very unfaithfulness is but a pointer to the kind of life that should be possible between people.

In the context of such a view of the world the business of having children has particular moral significance. For children are the sign that hope is stronger than despair in such a world -- and remember Christians believe that there is plenty to despair about in the world. Please note: I am not suggesting that Christians believe that our hope is in our children, as that would be blasphemy, but that our children are a sign of the kind of hope our faith in God gives us.

Put differently, children serve to anchor us in history. The temptation for Christians is to always think that God's salvation is beyond time or at least abstracted from time. Through our obligation to have children Christians are bound in time as they form communities that make clear their conviction, God is working in the world to form his kingdom of peace and justice. Thus our commitment, indeed obligation, to have children is our pledge that our salvation is not ahistorical, but takes place through the contingencies of history.

Now you may well think you do not need all this theological exposition to make a very simple point. After all with a slight misuse of Auden's "Existentialists declare/That they are in complete despair,/Yet go on having children." ("Under Which Lyre"). It is certainly not my intention that the views about children I

am trying to make clear are only limited to Christians, but rather I am simply trying to say what I take Christian conviction to entail.

However, there is another aspect of Christian conviction about having children that is not so obvious. The central documents of the Christian faith, which, oddly enough, have very little to say about sex, family, or children, do not make marriage and the family the first form of life. The Christians from whom we get the New Testament seem to have thought that the demands of the kingdom were such that singleness was at least of equal validity with marriage. Therefore, it was not incumbent on every Christian to marry or have children since, after all, the community was primarily to grow through conversion of those without. Put simply, Christians broke the assumption that marriage was a natural or moral necessity and thus made it a vocation. (And a vocation is not something you choose, but what you are called to.) They had to think about why they were having children, because their own beliefs now convinced them they were not obliged. I realize this would come as a great shock to most Christians today who assume that the truthfulness of Christianity depends on how well it reinforces their natural and cultural assumptions, but that is no great matter. As Chesterton pointed out, Christianity has not failed, it has just never been tried.

Christians assume that having children is not a natural event, but one depended on their deepest convictions. For example, many fail to notice that the Catholic condemnation of contraception, which many take to be an unwarranted imposition of biological necessity, was in its cultural context the attempt to take procreation out of the natural realm and subject it to the realm of freedom. For from such a perspective, children are not chosen, but viewed as the moral consequence of the obligations incumbent on the Christian called to the married life. Children are thus viewed as gifts necessary to sustain a people whose task

is to witness to the sovereignty of a God in a world that knows him not. We , therefore, are called upon to have children even though we know we cannot guarantee their safety.

Now all of this may still seem miles away from the question of in vitro fertilization, but I think it is relevant. For as the minister counsels the childless couple it is reasonable for him to try to help them find ways to have children. But the question is, how hard should they try? Nothing in the Christian attitude toward parenting requires that parenting should be defined biologically. Surely before you request medicine and science to develop techniques to allow you to have your biological children, it should be determined why it is so important that they be "biologically" yours. Especially in light of the indcision in defining the importance of having children in the first place. And as I suggested above they must realize that Christians do not assume that having children is a necessity for everyone in their community.

Moreover, it is not as if a childless couple among Christians is bereft of all forms and experiences of parenting. For if being a parent is first of all an office of a community, rather than a description of a biological process, even those without immediate children still have "parental responsibilities." Every community depends on educators, doctors, and countless other roles directly related to and in support of the community's commitment to its children. I am not trying to suggest that such activity is the same as responsibility for a particular child, but neither is it irrelevant for how one might understand one's parental responsibilities.

Even more important for Christians, given the specific commands for them to be concerned with widows and orphans and their responsibility to welcome the stranger among them, adoption surely seems to be the most appropriate strategy for childlessness. I seriously doubt, therefore, that Christian convictions about parenting



can supply the kind of intelligibility necessary to make the development of in vitro fertilization morally explicable. In particular Christians must surely be doubtful of any moral defenses in vitro fertilization that claim this technique as an extension of freedom from natural necessity. Such a claim from our perspective involves the pretentious assumption that there is no limit to the right of people to perpetuate themselves. From our point of view, in vitro fertilization may involve the most powerful form of necessity since it looks as if it is what we have done through our freedom. We thus forget that what always limits our freedom most is that which we impose on ourselves.

### 3. Biology and Parenthood

The position I have developed may sound particularly strange coming from a Christian, for many of the Christian critiques of in vitro fertilization have seemed to assume that the technique was wrong because it was "unnatural."

Thus Ramsey has argued "we procreate new beings like ourselves in the midst of our love for one another, and in this there is a trace of the original mystery by which God created the world because of His love. God created nothing apart from His love and without the divine love was not anything made that was made. Neither should there be among men and women any love set out of the context of responsibility for procreation, any begetting apart from the sphere of love. A reflection of God's love, binding himself to the world and the world to himself, is found in the claim He placed upon men and women in their creation when he bound the nurturing of marital love and procreation together in the nature of human sexuality. Thus, the Christian understanding of life stems from the second article of the Creed, not from the first or from facts or nature; and this is the source of the Christian knowledge than men and women would not put radically asunder what God joined together



in creation. Thus a Christian as such, intends the world as God intends the world...And in human procreativity out of the depths of human sexual love is prefigured God's own act of creation out of the profound mystery of his love revealed in Christ. To put radically asunder what God joined together in parenthood when He made love procreative, to procreate from beyond the sphere of love (AID, for example, or making human life in a test-tube), or to posit acts of sexual love beyond the sphere of responsible procreation (by definition, marriage), means a refusal of the image of God's creation in our own." <sup>6</sup>

Ramsey's view seems to be committed to thinking that biological procreation must be the only way Christians should try to become parents. Surely that is a strange conclusion, for pressed stringently it would make adoption problematic. Moreover, as Ramsey's own position assumes, biology is never simply biology but the appeal to the "natural" way is but a form of human intentionality. In other words, one can never just have sex as if it is a natural given, but rather all sex is "unnatural" insofar as it is formed by human intentions. Even if these objections are not decisive, however, it still remains unclear why Ramsey would exclude in vitro fertilization on these grounds, since it can, as Toulmin has recently suggested, be interpreted as an extension of what we are already doing through AIH (ie. both being attempts to aid couples to produce their biological children).<sup>7</sup>

I suspect that Ramsey has already anticipated the force of that objection and that is why he has not used the issues raised in the above quote in his recent arguments against in vitro fertilization.<sup>8</sup> Instead, he emphasizes the possibility of damage to the fetus and child and the assault such a procedure represents against the family and women in particular.

Ramsey's arguments in this respect are the attempt to find grounds to say in vitro fertilization represents or involves inherently wrong behavior. Underlying

his arguments, however, is profound doubt whether our culture, in the absence of any shared assumptions about the place of children in our lives, has the wisdom to control such a technique. In other words Ramsey's search for a knock-down argument against in vitro fertilization is an attempt to take the issue out of the realm of judgment as he fears we lack the wisdom to utilize it in a morally worthy manner. In contrast, I suggest that the issue is exactly the symbolic significant of in vitro fertilization. But Ramsey may well be right that the development of such a technique indicates that as a culture we lack an appropriate sense of parenting to guide its use, apart from any moral determination regarding the laboratory technique.

I suspect also that Ramsey's strategy is the conscious attempt to find arguments that will serve as secular analogues for his religious conviction. His religious assumption -- "what God has joined together let no man put asunder" -- can and ought not be made the basis of public policy. As a result he tries to resort to liberal assumptions against harm and "informed consent" to who in vitro fertilization violates both. For all of Ramsey's polemical brilliance, I think it fairly obvious that he has not shown that the "harm" or potential "harm" involved in in vitro fertilization renders the procedure inherently immoral: nor has he shown how the condition of "informed consent" has been violated.

Having thus criticized Ramsey in my view there is much wisdom in his understanding of the importance of the "biological" context of parenthood. For sex properly formed may in fact be an important condition for the development of the intimate bond we think significant to prepare us to claim our children as our own. His mistake is to argue that it is the necessary condition for such claiming. We forget that one of the great moral advances of our civilization is parents' willingness to claim their children as their own. In particular, one of the most difficult tasks of any culture is encouraging males to accept responsibility for their children. Ramsey may well be right that once procreation is severed from

sexual intercourse the basis for accepting the responsibility for parenthood becomes problematic. At the very least, once that separation has occurred, some very substantive convictions are needed to direct us to have appropriate attitudes toward those beings that present themselves to us as our children.

Indeed as I have tried to suggest above exactly because Christians broke the natural and moral necessity of procreation that their own commitments to children become so important. They learned children were not theirs, but God's. Therefore, not even biology could determine ownership, as children were not their to own. Rather they find themselves pledged to their children because of the depth of their conviction about the God who has called them into being. And Ramsey may be right if you believe that and our culture no longer provides a moral account to assure parental responsibility.

I do not wish to deny the importance of biology providing the medium for "bonding" between mother and child. I cannot, however, accept the crude determinism that assumes when "bonding" has not occurred through nine months of pregnancy mother and child are both under a decisive disadvantage. Biology may help us learn to be parents, but to know how to respond, use, and form our biology we must be guided by a moral portrayal of parenting that cannot be biologically derived.

There is a new movement to educate our youth to "parenting" in the public schools. The secular criteria for good parenting cannot possibly take account of the forgoing description of responsibility to God in the roles we assume as parents, yet the biological description is insufficient. It will, therefore, be extremely interesting what moral presuppositions will or can inform programs aimed at "educating future parents." I suspect the general assumption will be that "if you want to have children then this is the way to be fairly successful at it" thus assuming that the reason to have children is a "private" matter not open

to moral discourse. Rather all that matters is that one be emotionally and materially prepared for the "responsibility."<sup>9</sup>

#### 4. Medicine, Science, and Religion

One reasonable response to the kind of position I develop is to say, "All this is simply beside the point. What we are talking about is not philosophical or theological presumptions behind parenting. We are talking about the development of a technique derived from medicine's traditional commitment to alleviate the distress of patients. Some women cannot have children because of blocked fallopian tubes. All we are trying to do is provide them with the means to reproduce. Surely you Christians, in spite of your odd views about parenting, see the value in a doctor trying to help people do what an accident of nature prevents them from doing."

Without trying to develop it my first reaction to this possible response is to ask if the assumptions about the aim of medicine are in fact correct. Is the task of medicine simply to provide the means to help people accomplish certain ends irrespective of what those ends are? Without denying that medicine often does that, it has also been assumed that medicine should be governed by an internal ethic that makes it immune from consumer demand. All needs medically do not count equally. If the aim of medicine is health, then that surely involves moral assumptions about what and how the physician aids patients.

Moreover, even if the problem of "childlessness" is properly understood to be a "medical problem" then why is in vitro fertilization assumed to be the most effective therapy? Why do we not instead direct our attention to the development of implantable artificial fallopian tubes? For all I know we may already have such devices. Indeed, the lack of discussion concerning alternative therapies makes one suspicious about whether the purpose of this research is limited to its therapeutic ends. Any intellectual knows the attraction of an "interesting



problem." Can we discount that such interests are present in our assumed therapeutic interest in in vitro fertilization?

This perspective might be interpreted as religious people again trying to restrict the progress of science because they fear the consequences. It is certainly true that religious people have often said "no" to science because they are afraid that science will remove the "mystery" of life and thus make religious belief unintelligible. Or they assume, in the absence of any sure way to know God's will, "nature" is our only indication of God's intentions and to fool with "nature" is thus to disturb God's law. From my remarks above, it should be clear I do not share this understanding of nature's relation to God; nor do I think that faith in God is a correlative to assuming that life is finally a "mystery." In contrast I much prefer to think of life as interesting, an adventure that we can risk because, not in spite, of our faith in God. The only mystery the Christian faith has a stake in preserving is the mystery of God's forgiveness. All other "mysteries" are but puzzles next to that one.

Rather than treat this again as an issue of religion and science, it should be considered in terms of what ends of community should guide our scientific endeavors. Any conflict between religion and science concerning such matters as in vitro fertilization does not lie in the actual technique itself, but in the claim that science is autonomous and not susceptible to guidance or judgment from external authorities. That is indeed a claim that Christians cannot help but challenge. As members of an institution that also claims total loyalty, we recognize other counter-churches. Christians insist that science, practiced morally, must be at the service of community -- not its master.

The most important response, however, to the claim that medicine's attempt to develop in vitro fertilization is solely to provide individuals with a necessary therapy, is that such an intention is unjust. For surely the man-hours

and resources necessary to develop such a technique is hardly worth the results. This may sound like a harsh judgment to those who want children but are prevented from doing so, but in the classic words of Jimmy Carter, "life is unfair." Surely amid the immense needs of our society, resources can be better spent than developing techniques to allow a very small percentage of women to experience pregnancy. I simply do not understand why that particular problem should be thought so severe that resources should be given to it before we have, for example, a cheap and effective clotting factor for hemophiliacs.

## 5. Conclusion

I have not dealt with such issues as the status of the blastocyst,<sup>10</sup> discarded conceptus, how such procedures may produce damaged human beings, or possible misuses of the technique. I have not done so because others have already discussed such matters, but also because I do not think such issues have the same kind of theological interest. Also, I have not dealt with such matters as they seem to me to direct our attention to the wrong place. For in spite of the theological cast of my argument I hope my position is a call to take seriously what is really at stake in in vitro fertilization -- namely, common sense.

Of course, as has often been pointed out, nothing is more uncommon than common sense. If we but listen to our common sense as a society I believe we should not fund in vitro fertilization though neither should we prohibit those who wish from pursuing in vitro fertilization research. In my opinion no Christian should support or engage in such research as it can only appear to us a pretentious and unjust attempt to substitute biological identity for the moral convictions that should be the substance of familial identity.<sup>11</sup>

## Footnotes

<sup>1</sup> I think it would be extremely interesting to know when the field of "ethics" or the job of the "ethicist" began to be understood as an independent and self-sufficient activity. The Roman Catholic community has "moral theologians" who had clearly defined tasks correlative to definite institutional needs of the church. But it was not assumed, though it tended to be the practice, that "moral theology" was thereby a coherent or independent intellectual area. In our own context I suspect the idea that "ethics" is an intelligible field is not the result of a coherent intellectual and social position, but an attempt of a confused society to substitute reflection, to create more "experts", for morally substantive convictions.

<sup>2</sup> Alasdair MacIntyre has argued forcefully that the dominance of Kantian pre-suppositions in contemporary moral philosophy has resulted in a failure to acknowledge the intellectual and moral significance of the moral pluralism of our society. In an attempt to provide grounds for moral agreement between people with different beliefs modern moral philosophy has attempted to make "beliefs" irrelevant to moral judgment, self or character secondary to moral decisions. As a result moral experience has been distorted as we have been left with insufficient conceptual tools to understand what has happened to us morally. The current emphasis on "rights" as the conceptually primitive or bedrock moral notion is but a further indication of this tendency. For MacIntyre's position see his, "How to Identify Ethical Principles", a paper prepared from the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

<sup>3</sup> For a more extended presentation of this position see my Character and the Christian Life (San Antonio: Trinity University Press, 1974); and Vision and Virtue (Notre Dame: Fides/Claretian, 1975).

<sup>4</sup> Leon Kass, "Ethical Issues in Human In Vitro Fertilization, Embryo Culture, and Research, and Embryo Transfer," Paper prepared for the Ethics Advisory Board, Department of Health, Education, and Welfare.

<sup>5</sup> For a more extended discussion of this point see my Truthfulness and Tragedy (Notre Dame: University of Notre Dame Press, 1977), pp. 147-163. "Sex and Politics: Bertrand Russell and 'Human Sexuality,'" Christian Century, XCV, 14 (April 19, 1978), pp. 417-422; and "The Moral Value of the Family," Commonweal (Forthcoming).

<sup>6</sup> Paul Ramsey, Fabricated Man (New Haven: Yale, 1970), pp. 38-39.

<sup>7</sup> Stephan Toulmin, "In-Vitro Fertilization: Answering the Ethical Objections," Hastings Center Report, 8, 5 (October, 1978), pp. 9-11

<sup>8</sup>Ramsey, "Testimony on In-Vitro Fertilization," Ethics Advisory Board, Department of Health, Education, and Welfare.

<sup>9</sup>This paragraph and much else in this paper I owe to Anne Harley Hauerwas.

<sup>10</sup>Though I do not wish to make much of it I find the language that the blastocyst or conceptus has "some value" to be a conceptual mystification. They obviously want to say that this is human life and thus should be treated with care, i.e., it has "some value," but I simply fail to understand how something can have "some value." It either has value or it does not. I suspect that the language of "value" simply fails adequately to provide the kind of discourse to understand why we feel hesitant to treat the human conceptus any way we wish for the good ends of science.

<sup>11</sup>It might appear that the position I have developed is antithetical to the Jewish understanding of the importance of biological identity for the family. For example, Onan's sin was not, as the Catholics assume masterbation, but his refusal to be open to keeping his brothers name alive in Israel. There is no doubt a stronger emphasis on familial continuity among Jews than for the Christians, but for both the "biology" remains secondary to the family understood as a religious and moral institution.



HUMAN IN VITRO FERTILIZATION: A JEWISH PERSPECTIVE

Sid Z. Leiman, Ph.D.



## I. Introductory Remarks

Since I am neither a biologist nor a lawyer, but rather a professor of Jewish history and literature with a strong interest in Jewish ethics, I have assumed that the invitation extended to me to address this august body was occasioned in large part by a desire to bring to bear Jewish teaching on the issue of human in vitro fertilization. I wish to state at the outset that from my perspective your extending invitations to historians and analysts of religious ethics is in itself a noble and productive enterprise. The various ~~faiths~~ are repositories of the ethical teaching of the past, and we have much to learn from the ancients with regard to contemporary ethical concerns. As Collingwood once said: "The value of history, then, is that it teaches us what man has done and thus what man is."<sup>1</sup> My role here this morning is not that of an advocate, but rather that of a resource person whose comments are intended to inform, hopefully to stimulate, but not necessarily to persuade. Whatever I have to say is informed by Jewish teaching, but ultimately reflects my own reading of the sources and -- unless indicated otherwise -- my own opinion. I am not here as an official representative of a particular church or synagogue or institution. Regarding in vitro fertilization, it is a difficult enough task to represent one's self.

## II. The Issues

For heuristic purposes, I have found it convenient to structure this presentation in scholastic form. I shall list ten sets of questions, and then attempt to provide Jewish responses, however brief, to those questions. The answers to the last two questions will, in effect, summarize several Jewish perspectives on in vitro fertilization, and incorporate some personal opinion as well. At best, whatever I say is provisional, even with regard to Jewish teaching, for Jewish teaching is an ongoing process. And one can say with certainty regarding in vitro fertilization that more remains to be said than has been said. I turn to the questions:

1. Are not in vitro fertilization and embryo implantation an interference with nature, and thus, ipso facto, to be viewed with suspicion? Is not sexual intercourse the only natural setting for procreation? Will not in vitro fertilization and embryo implantation lead to various kinds of abuse ranging from host-mothering-for-profit to the public auction of celebrity ova and sperm?
2. Human in vitro fertilization experimentation as presently practiced involves the fertilization of ova that will deliberately not be brought to term. Should such life be created and aborted in order to advance science? Should such life be created and aborted in order to enable the infertile to become fertile?



3. If an ovum is provided by X, and is then fertilized in vitro, and then implanted in Y, who brings the fetus to term, who is its legal mother?
4. In cases of surrogate mothers, who would have the right to decide for abortion or amniocentesis?  
Would either the provider of the ovum or the surrogate mother have a right-of-refusal?
5. X and Y are sisters happily married to their respective spouses. X is infertile, and in order to procreate, agrees to the implantation into her uterus of a fertilized ovum of Y. X's husband has provided the sperm for the in vitro fertilization. Is the husband guilty of either an incestuous or adulterous relationship?
6. Assuming an in vitro fertilized ovum could be brought to term in vitro, would the donor of the ovum or the scientist who conducted the experiment be the legal mother?
7. If a conceptus is brought to term in vitro, what would be his or her legal birthday? Consequences here can sometimes be a matter of life or death, e.g. determining whether or not it was a minor or adult who committed a murder, or whether or not someone was eligible for the draft.

8. If a scientist engages in in vitro fertilization without the prior consent of the male and female donors, who is legally and morally responsible for the conceptus when brought to term? Is rape possible in vitro?
9. Should the Federal government support human in vitro fertilization research?
10. Should the Federal government subsidize human in vitro fertilization and embryo implantation as a health care delivery service? Is infertility a disease requiring medical attention? Is making the infertile fertile therapeutic?

### III. Discussion

From a Jewish perspective, much of medical practice, and certainly surgery is a kind of interference with nature. But such interference is welcome when it is therapeutic. In the Midrash (Jewish homiletic literature from the 2nd through the 12th centuries) we are told about Ishmael and Akiba, two distinguished 2nd century Palestinian rabbis, who were walking through the streets of Jerusalem when they chanced upon a sick man.

The sick man asked: "Masters, how can I be cured?" The rabbis responded: "Take such and such medicine and you will be cured." The sick man then asked: "And who afflicted me with disease?" "The Holy One Blessed be He," replied the

rabbis. The sick man asked once again: "Do you then interfere in matters that are not your concern? God afflicted and you heal?" The rabbis responded with a question: "What is your occupation?" The sick man responded: "I am a tiller of the soil; and I prune trees." "But who created the soil and the trees," asked the rabbis. "The Holy One Blessed be He," answered the sick man. The rabbis continued: "Did you then interfere in a matter that is not your concern? He created the trees as they are, and you have the audacity to prune them?" The sick man responded: "Were I not to weed the field and prune the trees, it would bear no fruit." "So too," answered the rabbis, "with regard to the human body. Without proper medical care it cannot function properly."<sup>2</sup>

Another rabbinic passage tells the following story:

When Hillel (a first century rabbi and contemporary of Jesus) completed the lesson with his disciples, he accompanied them on their way. They asked him: "Master where are you going?" He replied: "To perform a religious duty." "Which religious duty," they asked. Hillel answered: "I am going to take a bath." "Is taking a bath a religious duty," they asked? Hillel explained: "If the statues of the Emperor in the public domain are regularly scraped and cleaned, how much more so should I, who am created in the divine image, take care of my body."<sup>3</sup>

Thus, classical Judaism looked kindly upon the internal and external care of the body. Interference was welcome when it was beneficial to the patient.

While sexual intercourse was viewed as the natural setting for procreation, it was not the only one. Thus, Jewish sources from as early as the fourth century discuss efforts upon the part of some rabbis to create humans without engaging in sexual intercourse.<sup>4</sup> Indeed, the Talmud claims that the rabbis succeeded in their efforts! Regarding artificial insemination, the rabbis discussed its legal implications as early as the fifth century of common era.<sup>5</sup> The rabbis did not proscribe efforts to create humans without engaging in sexual intercourse, nor did they view artificial insemination as being unnatural in a pejorative sense. In general, it is worth noting that classical Judaism viewed sex and procreation as independent values.<sup>6</sup> Sexual intercourse during pregnancy, for example, was a wife's privilege and a husband's duty. It mattered not that she was pregnant. Similarly, procreation was viewed as a value independent of the sexual act.<sup>7</sup> Thus, it is not surprising that many contemporary rabbis find human in vitro fertilization palatable, when warranted. This is not to say that rabbis have no preferences. To be sure, they viewed natural sexual intercourse as the primary means of procreation; but they acknowledged other possibilities.

Regarding possible abuse, it would be the responsibility of the Federal, state, and local governments to prevent or control serious abuse. But this should in no way lead us to throw out the baby with the bath-water. Drug abuse abounds in this country but no one is seriously considering



abolishing drugs. In vitro fertilization may be likened to a box of matches, a kitchen knife, and an automobile. When used properly, they are a boon to mankind; when used improperly, they are destructive. It is the manipulator, and not the object, that must bear the blame for any wanton destruction.

Regarding question 2, much depends on how one views the moral worth of the conceptus in its earliest stages. Some Jewish authorities rule that during the first 40 days of gestation, the conceptus has little or no moral status, and therefore could be aborted for any constructive purpose, such as medical experimentation.<sup>8</sup> Other, more stringent Jewish authorities accord moral status to the conceptus from the moment of conception on. They advocate confining human in vitro fertilization to one ovum at a time (instead of the present practice of extrapolating and fertilizing numerous ova), thus obviating the wanton destruction of unused fertilized ova.<sup>9</sup>

Questions 3-8 are really all of a kind. What they serve to underscore is the legal ambiguity that abounds in in vitro fertilization and in embryo implantation. In Judaism, no decision regarding such a weighty matter as in vitro fertilization would be rendered until all the legal consequences were explored and resolved. It seems to me that the Department of Health, Education, and Welfare should not approve a research application in these areas unless the desired or expected results are free and clear of legal encumbrance and ambiguity. Thus, if the desired result of an experiment

is an embryo transplant which will be brought to term by a surrogate mother, the legal status of the infant-to-be needs to be determined before the experiment is funded, not after. Similarly, if the desired result of an experiment is a conceptus brought to term in vitro, a new legal definition of birth needs to be promulgated before the experiment is funded, not after. Another sample of legal ambiguity comes from a less pressing area, but one that nonetheless merits mention here. I have seen numerous discussions of human cloning. Inevitably, it is argued that one of the important benefits of human cloning will be the availability of spare parts for organ transplantation. If what is intended is the creation of human clones whose organs would be designated for transplantation purposes, I fail to see by what ethic or law any clone could be designated a donor rather than a recipient. And if experiments are being undertaken whose intended result is the cloning of a human being, we had better legislate now regarding the rights and privileges of such clones.

Instead of responding directly to each of the questions 3-8, which at this stage of Jewish discussion would in any event be premature, I should like to focus on the question of surrogate mothers, and hopefully, a Jewish response to some of the questions will begin to emerge. The earliest Jewish discussion relating to embryo implantation dates back to 1928, and was authored by an East European rabbi<sup>10</sup> (Kamelhar) who reports that the status of child born from an ovarian transplant was discussed at a medical conference held in Chicago in 1911.<sup>11</sup> Was its mother the donor of the organ,

or the recipient mother who brought the child to term? After drawing several dubious analogies to talmudic passages, the rabbi ruled (in theory, of course, since he was not involved in the case) that the recipient of the ovary was the child's legal mother. He reasoned that since in the case in question fertilization occurred after the transplant, clearly it was the recipient's ovum that had been fertilized. And in humans, "the seed of the father and the mother who is impregnated and gives birth is decisive." The learned rabbi was perhaps a poor biologist (for while it is clear that a transplanted ovary becomes the property of the recipient, it is by no means clear that an ovum fertilized after the transplant is to be genetically related to the recipient); but the principle he enunciated seems to be clear: parentage is determined by genes. The providers of the sperm and ovum that form the zygote are the legal parents of the conceptus. Kamelhar did not envision the possibility that one mother could provide the genes and another could provide the locus for impregnation; nor is it altogether clear how he would have ruled in such a case. It may well be that he would have drawn a distinction between the implantation of a fertilized and an unfertilized ovum, motherhood being determined genetically in the former case and by locus in the latter case. Recent rabbinic discussion is divided on the issue,<sup>12</sup> but there is every indication that at least in the case of implantation of a fertilized ovum the emerging consensus will be that



motherhood is determined genetically.<sup>13</sup> This does not rule out surrogate motherhood. It simply indicates that from a Jewish perspective surrogate motherhood does not necessarily carry with it the maternal obligations and privileges (e.g. filial responsibility) that genetic motherhood does. Judaism clearly would not look kindly upon surrogate motherhood when it is resorted to "as a convenience in order to avoid the encumbrances of pregnancy."<sup>14</sup> But such moral judgments, it seems to me, are not the concern of public policy makers. It is the business of the United States government to protect the rights of, and to prevent tangible harm to, its citizens. It is not the business of the United States government to comment upon the morality or immorality of surrogate mothers-for-profit, so long as no one's rights are compromised and all agreements entered into are by mutual consent, and actionable in a court of law. From an American perspective, I see little difference between a wet nurse and a surrogate mother, assuming procedures are perfected so that there are no extraordinary dangers to the surrogate mother's health.

In recent rabbinic discussion, parallels are drawn between artificial insemination and embryo implantation.<sup>15</sup> Recipients of donated ova or sperm assume legal responsibility for their progeny only by contract.<sup>16</sup>

From a Jewish perspective rape and incest are crimes against persons; they are integrally bound up with sexual intercourse. Where there is no physical contact between



male and female, there is neither rape nor incest.<sup>17</sup> Thus, the mad scientist who expropriates an ovum and fertilizes it in vitro has committed an actionable offense and can be sued by the mother and child for child support, and perhaps for other damages as well, but he has not committed rape.

Questions 9 and 10 bring me to my conclusions:

Research in human in vitro fertilization for purposes of enabling the infertile to become fertile should be supported by the Federal government, if:

- a. Appropriate preliminary research has been done on non-human primates.
- b. Risk-benefit analysis is favorable. Ideally, the state of the art should be that no greater risk be involved for the conceptus and the mother than in normal pregnancy and childbirth.
- c. Informed consent of all participants is obtained.
- d. Appropriate liability and compensation for research related injuries is assured.
- e. The legal consequences of the desired or expected results are free and clear of encumbrance or ambiguity. (Indeed, it would be appropriate for the Ethics Advisory Board to invite legal experts -- who know how and to what extent ethical concerns can be translated into law -- to offer their input into the guidelines that will ultimately emerge from the Ethics Advisory Board.)

f. Human zygotes and embryos are not destroyed wantonly.

The Federal government should subsidize health care delivery services for the needy, as for example, through medicaid. These services should include in vitro fertilization and embryo transplant, if such procedures are necessary in order to render an infertile patient fertile, and if such procedures prove to be safe.<sup>18</sup> It would be a sad commentary on the American ethos if federal funds could subsidize the taking of human life (i.e. therapeutic abortion), but not the creation of human life (i.e. therapeutic conception). I am aware that some strict constructionists will not view infertility as a medical need, and its cure as therapeutic. They overlook the fact that it was to the physician that the infertile have turned for centuries seeking a cure. Now that physicians can at least in some instances administer the cure, it is hardly the time to label that cure non-therapeutic. Surely, in vitro fertilization and embryo transplant are a cure for dis-ease, if not disease. The rabbis put it this way: Four are considered as if they were dead: the poor, the blind, the diseased, and the childless.

## NOTES

- 1  
R. G. Collingwood, The Idea of History, New York: Oxford University Press, 1956, p. 10.
- 2  
Midrash Temurah in A. Jellinek, ed., Bet ha-Midrash, Jerusalem: Wahrmann Books, 1967, vol. 1, p. 107.
- 3  
Midrash Rabbah: Leviticus XXXIV:3, in H. Freedman and M. Simon, eds., The Midrash, London: Soncino Press, 1939, vol. 4, p. 428.
- 4  
E.g., Babylonian Talmud, Sanhedrin 65b. In general, see A. Rosenfeld, "Religion and the Robot," Tradition 8 (1966), number 3, pp. 15-26.
- 5  
E.g., Babylonian Talmud, Hagiqah 14b-15a. In general see "Artificial Insemination in Jewish Law," in F. Rosner, Modern Medicine and Jewish Law, New York: Yeshiva University Press, 1972, pp. 89-106.
- 6  
See D. M. Feldman, Birth Control in Jewish Law, New York: New York University Press, 1968, pp. 21-105.
- 7  
See, e.g., Samuel b. Uri Shraga Phoebus (17th century), Beth Shemuel 1:10 in the standard editions, J. Karo, Shulhan Arukh, Eben ha-Ezer, chapter 1.
- 8  
Feldman, op. cit., p. 266, notes 79 and 83.
- 9  
J. D. Bleich, "The Problems of Creating a Test-Tube Baby From a Jewish Perspective," (Hebrew) Or Hamizrach 27 (1978), p. 14.
- 10  
J. Kamelhar, ha-Talmud u-Maddaey ha-Tevel, Levow: Czcionkami Drukarni, 1928, pp. 44-45.
- 11  
The rabbi gives no details regarding the identity of the medical society that convened the conference, nor does he provide the names of the participants. That ovarian transplantation was a topic of discussion in Chicago in 1911 is clear from F. H. Martin, "Ovarian Transplantation in Lower Animals and Women," Surgery, Gynecology and Obstetrics 13 (1911) 53-63. Martin practiced in Chicago, though the

paper on ovarian transplantation was read before the American Gynecological Society on May 24, 1911, in Atlantic City. It may be that the rabbi (or his informants) mistook Martin's place of residence for the location of the American Gynecological Society conference.

12

See, e.g., B. Z. Safran, Sheelot u-Teshuvot Harabaz, Jerusalem: Mosad Harav Kook, 1962, pp. 204-25; M. Klein, Sheelot u-Teshuvot Mishneh Halakhot, vol. 4, Tel Aviv: Makhon Mishne Halakhoth Gedoloth, 1970, responsum 249; E. J. Waldenberg, Sheelot u-Teshuvot Tzitz Eliezer, vol. 10, Jerusalem: Itah, 1970, responsum 25, chap. 26, paragraph 3, p. 167; I. Liebes, "On Organ Transplantation," Noam 14 (1971) 28-111; and J. Gershuni, "The First Test-Tube Baby in the Light of the Halakhah," (Hebrew) Or Hamizrach 27 (1978) 15-21.

13

So personal communications from numerous rabbinic authorities including Rabbi Dr. Moses D. Tendler of Yeshiva University. On the genetic determinant of motherhood, see especially A. J. Horovitz, Sheelot u-Teshuvot Tzur Yaakov, Bilgoray: Kronenberg, 1932, responsum 28, end, who writes: "Do the female generative organs create the baby? They are simply a means for housing the conceptus. The essential factor in the creation of a baby is the seed of the father and the mother, as spelled out in the Talmud."

14

J. D. Bleich, "Host-Mothers," in his Contemporary Halakhic Problems, New York: Yeshiva University Press, 1977, p. 106.

15

See the references cited above in notes 9, 12, 13 and 14.

16

See M. Feinstein, Iggerot Moshe, Even ha-Ezer, New York: Sinai Offset Co., 1961, responsum 10, end.

17

See M. Feinstein, Iggerot Moshe, Even ha-Ezer, vol. 2, New York: Gross Brothers, 1963, responsum 11.

18

Cf. the opinion rendered by the Sephardic Chief Rabbi of Israel, Rabbi Ovadiah Yosef, as reported in the Jewish Telegraphic Agency Daily News Bulletin, August 16, 1978.

19

Babylonian Talmud, tractate Nedarim 64b.



TESTIMONY ON IN VITRO FERTILIZATION

Paul Ramsey, Ph.D.



# Testimony on In vitro Fertilization

## Ethics Advisory Board

Department of Health, Education and Welfare

submitted by

Paul Ramsey

My name is Paul Ramsey. I am the Harrington Spear Paine Professor of Religion at Princeton University. My field of scholarly specialization is ethics and social philosophy--in particular, though not exclusively, Christian ethics. My credentials for submitting this testimony are the fact that as long ago as 1972 I wrote a two-part article on in vitro fertilization published in the Journal of the American Medical Association,<sup>1</sup> that for the past fifteen years I have written extensively in the area of medical ethics,<sup>2</sup> that I am a member of the Institute of Medicine of the National Academy of Sciences, and a founding Fellow and member of the Board of Directors of the Institute of Society, Ethics and the Life Sciences, and was once awarded an honorary doctorate of science by the Worcester Polytechnic Institute (of which I am inordinately proud).

To state my considered judgment in advance of the

reasons for it: in vitro fertilization and embryo transfer should not be allowed by medical policy or public policy in the United States--not now, not ever. I venture no comment on whether sufficient "animal work" has been done, by scientific standards, for this technology safely to be applied within general practice or in trials on human beings. That question and such like questions you will explore with scientific experts. I limit myself to basic ethical and policy considerations that any knowledgeable citizen can understand; and it is in this capacity that I submit this written testimony.

It is my conviction that the Ethics Advisory Board, the Department of Health, Education and Welfare, the National Institutes of Health and the Congress of the United States--and, in absence of action from these Federal sources, the medical profession itself if it has any remaining power to enforce standards or the legislatures of the several States--should take appropriate action to the extent of their jurisdictions to stop embryo manipulation as a form of human genesis.

I am not unmindful of the gift of a child this procedure promises to women with oviduct blockage--a promise now once delivered, with possibly more soon to come in Great Britian. Still there are, I judge, conclusive reasons



for not continuing these experimental trials and for not allowing the procedure to become standard practice in the United States.

I offer four reasons in support of this verdict:

(1) the need to avoid bringing further trauma upon this nation that is already deeply divided on the matter of the morality of abortion, and about when the killing of a human being (at tax expense) can occur; (2) the irremovable possibility that this manner of human genesis may produce a damaged human being; (3) the immediate and not unintended assault this procedure brings against marriage and the family, the immediate possibility of the exploitation of women as surrogate mothers with wombs-for-hire, and the immediate and not unintended prospect of beginning right now to "design" our descendents; and (4) the remote--but still very near--prospect of substituting laboratory generation from first to last for human procreation. We ought not to choose--step by step--a world in which extracorporeal gestation is a possibility. Since I wish to testify to things distinctively characteristic of embryo manipulation, reasons (2), (3), and (4) are more significant, in my opinion.

I

Nevertheless, the abortion issue cannot simply be

passed by. Millions of U.S. citizens who oppose abortion will bring the same moral objection against in vitro fertilization because of the numerous "discards" the procedure requires.

Let me be clear about this first point. I am not speaking of traditional Roman Catholics only. I refer also to the growing number of "evangelical" Protestants whose voice in Washington is the Christian Action Council. I also have in mind the hundreds of thousands of our fellow citizens in the "mainline" Protestant churches who conscientiously oppose abortion despite their leaders. I also have in mind Orthodox Jews and many Conservative Jews and all Mormons, and for all I know many humanists as well, who agree in this common opposition. We are a pluralistic society, like none other in the world.

I do not here open the question of the morality of abortion. Instead, I mean only to call attention to the additional trauma that will be brought upon a nation morally divided on this issue if any Federal funding by the Department of Health, Education and Welfare or the National Institutes of Health goes to support in vitro fertilization as a form of human genesis, or to support any research tending in that direction. Millions and millions of our fellow citizens do not want their pockets

picked by the Internal Revenue Service if any portion of their income taxes go to support what they sincerely believe to be repeated abortions.

The Supreme Court has declared that public policy in regard to funding abortion is not a question of constitutional right, but rather a matter to be determined by the democratic processes of Federal, State, and even municipal legislation.<sup>3</sup> The Ethics Advisory Board will play a crucial role in determining public policy by "administrative law," not by legislation. Your hearings on in vitro fertilization may eventuate, or may not eventuate, in a policy that uses citizens' taxes for purposes to which vast millions are conscientiously opposed. I urge you to consider that constitutionally, on this point alone, you have the legal authority to make whatever "value judgement" or public policy judgement you wish to make. It is within your power of recommendation to encourage or discourage, to allow or to prohibit, the funding of the number of "discards" that are required in the course of in vitro fertilization as a new form of human genesis. To this first point I add the following. To me, at least, it would be significant to find out--if Dr. Robert G. Edwards or Dr. Patrick C. Steptoe could be called to testify--how many, if any, of their monitored trials

(from 60 to 200 "failures" have been estimated) have required abortion after the embryo had become, technically, a fetus; and how many, if any, monitored trials required abortion at a stage after viability, which the Supreme Court in Wade declared the States could go so far as to prohibit.

Whatever policy the EAB-DHEW (or the Congress) promulgates, it is clear that the several States can constitutionally prohibit in vitro fertilization in their jurisdictions, as many have done in the case of fetal research. I would prefer a national solution flowing from the recommendation of the Ethics Advisory Board or by Congressional legislation. My plea is that the consciences of millions of our fellow citizens ought not to be additionally burdened by forced cooperation, through funding, in believed evil. You would not want any one of these millions of people to be your friends or neighbors if they thought it right to kill 60 or 200 human lives in order to give birth to one. You would want them to resist, instead of tacitly consenting to, such a spectacular increase of "elective abortions." So my first point is that a prudent medical and public policy on this matter should not, for the sake of so few for whom there are other alternatives including improved oviduct reconstruction, further exacerbate our "civil war" over the morality of abortion.



As a matter of national public policy, I ask you to consider the result of allowing embryo manipulation to become first a trial and then standard medical practice. Already it is the case that Federal and State "conscious clauses" allowing freedom from participation in elective abortions for individuals and medical institutions are not working. For them to be effective would require "affirmative action" such as is now devoted to racial and women's rights.<sup>4</sup> Pressures are already building up for publically funded HMO's to provide medically unnecessary abortions and sterilizations, which present law does not require. These pressures come from the consumers of these services; the providers also have economic and medical interests in showing that HMO's practices fulfill community demands. So I ask: if the Ethics Advisory Board and DHEW approves, and if then the Congress negligently approaches (or lets research continue on) embryo manipulation and discard, what obstacles will this raise against the adoption of a national health plan in which these procedures could become standard medical practice?

A judicious approach would surely be to exclude such procedures from among the medical procedures claiming public support or general approval. If any American supports a comprehensive national health plan, he or she should exclude in vitro fertilization, and other deeply devisive proposals, from such a plan. For the same reasons, we ought not to ask our conscientiously-opposed fellow citizens to support elective abortions

with their taxes. I see no other practical compromise that will not increase the polarization and tear further asunder the fragile moral fabric of our nation.

It may be objected that my argument from believed "moral contamination by taxation" does not hold because it would make every person's conscience his own government, and therefore would frustrate public policy on almost every matter. Here, I think, sound judgement requires us to distinguish between policies and funding that are overridingly in the national interest and those that are not. A person may believe, for example, that suicide is morally wrong and yet oppose any law against suicide. Since no one any longer believes that suicide is wrong because, among other things, it "deprives the king of a subject," the death of a person by self-willed destruction may not always be a matter of overriding national interest. Two authors (conservative Catholics, as it happens)<sup>5</sup> have used this consideration to argue that decisions to live or to die could well be left to be settled between a patient and his or her physician by legislation making the tort of treating a person against his or her expressed will (whatever it is, and however for these authors immorally suicidal) survive the deceased. Such tort legislation would privatize a possibly immoral decision involving no third party; that is to be preferred to the

States' and its peoples' involvement in "living wills" or "right to die" legislation. I judge that these authors feel deeply that the former policy is much to be preferred to believed moral contamination by euthanasia or near-euthanasia legislation brought upon the public at large.

I use this only as an analogy. The freely chosen death of an individual by (believably) immoral means or circumstances need not be regarded as a matter of national interest or public policy concern. Neither is enabling a woman to have a baby in the overriding national interest, unless one believes that hereby "the king" gains a needed "subject."

For another comparison, foreign policy and even bad wars are matters that require coercive taxation. Persons who during the Vietnam war withheld their taxes were doubtless to be admired for this form of "witnessing" protest, provided they were willing to bear the consequences of their action. "Curing" infertility in particular cases is an entirely different question, as are individual choices no longer to live by medical means. We are born and we die; the people of the United States go on, with little or no consequence from those personal events.

I am not suggesting that such outcomes are anything

other than profoundly important personally, and morally. But I do suggest that neither should become entwined with public policy. I urge the Ethical Advisory Board to consider that any tax funds to learn how to do in vitro fertilization in the United States across numerous "discards" is (1) profoundly conscientiously objectionable to millions and millions of our fellow citizens and (2) can in no way be deemed to be an overriding national interest worth making "tax objectors" of them.

I add also that any member of the Board who can wish this to become a "standard medical practice" must want both our present health care delivery system (which is largely funded) and any future national health plan to be profoundly oppressive to consciences. The argument will be--will it not?--that since rich women can afford this service, "distributive justice" requires us to provide it to poverty women as well, through Medicaid. Heretofore that argument--in the matter of abortion--has had behind it the fiscal consideration that otherwise it will cost more to care for children born in poverty. In future, the "distributive justice" argument will stand alone, no matter what the cost of perfecting and delivering this service, or the cost of having done so in supporting the children so produced. I don't suppose that in years to



come we are going to prohibit women on welfare from overcoming oviduct blockage, or refuse to fund this medical service, simply because of the cost in ADC payments. Of course, conscientious objectors to funding abortion or funding petri dish discarding do not think highly of this argument, since for them it is meaningless to speak of fairness in justly distributing an immoral practice. But I do urge its weight upon members of the Ethics Advisory Board who are charged with recommending the future direction which national medical practice should take.

Perhaps I have prolonged my reply to the objection too far. My main appeal is to ask the Ethical Advisory Board to consider the suppression and alienation from the community of this nation of the consciences of millions and millions of our fellow citizens if your approval and any tax funds are put into in vitro fertilization, embryo transfer--and embryo discard. I ask you to consider--with no prejudice in favor of "science"--whether approval of Vanderbilt's professor of Ob-Gyn, Dr. Pierre Soupart's application for funds is really worth the other moral and social costs that will surely be imposed upon this nation.

## II

My final three points do not touch upon the issue of

the morality of abortion, or Federal funding of it. The distinctive arguments I submit to you are, first, the irremovable possibility that this manner of human genesis may produce a damaged child and that this constitutes a conclusive argument against allowing such attempts to be made in the human community, in the United States or any other society.

One "successful" case does not settle the issue I am raising. Besides, who now knows that Louise Brown was a scientific accomplishment? Physical characteristics are not enough to show this.

Here I detour beyond my depth to invoke an analogy with amniocentesis. This procedure has been judged by medical authorities to be safe, no longer experimental. That verdict seems to be concentrated on the mother's safety, and on the unlikelihood that the procedure would induce spontaneous abortion. Incidentally, one percent chance of "false positive" diagnosis for the unborn child, i.e. one in one hundred, does not seem to one to be a negligible risk for the child. My point here, however, goes beyond the physical destruction of normal unborns instead of physically defective fetuses because of mistaken diagnosis. The point is rather whether the procedure of amniocentesis does or does not induce unknown and unknowable psychological

damage to the children who are saved from genetic abortion. Henry Nadler, M.D., wrote that, while amniocentesis detects gross anomalies, "There is no way, with present studies, our own included, of establishing, ten or fifteen years from now, if these children [the children saved from genetic abortion] lose 5 or 10 I.Q. points"; "The risks of 'induced' congenital malformations are difficult to determine and the subtle damage in terms of loss of intelligence is almost impossible to evaluate."<sup>6</sup>

The comparison with human genesis by embryo manipulation should be clear. No one knows the future of these children. We ought not to try to discover these truths by human experimentation upon them. But there is no other way to find out. The argument is conclusive, unless as a people we mean to make technical medical advance by creating our progeny at risk of unknown and unknowable damage from the procedure itself.

This would violate the primary principle of medical ethics, "Do no harm." To understand that this is the case, we have to distinguish clearly between the procedure in question and medical treatments given the "maternal-fetal unit" when both mother and fetus are actual patients. Sometimes procedures are necessary that are hazardous to the fetus (e.g. intrauterine blood transfusions), but the

life that is exposed to hazard stands also to be benefited. In such treatments, possible harm may be risked. Embryo manipulation is quite different: here the mother seeks a benefit; this benefit can be delivered only at some risk of grave injury to the future possible child. Oviduct reconstruction (now a much improved art) is by contrast a treatment that can be undertaken at no risk to another life than the one who elects the operation--since no other life has yet been conceived or will be manipulated.

In his series of articles in The New York Times<sup>7</sup> Walter Sullivan brought up another possibly deleterious outcome that is impossible to remove. Notably, he was quoting the British scientists. The eggs taken after superovulation of the female may not be those that would mature normally. The sperm that in natural reproduction reach their goal are "a highly selective sample," Dr. Edwards noted, "relatively free from genetic defects." There is no such "screening" in in vitro fertilization. The "screen" may be the opposite. Such subtle effects, Sullivan correctly concluded, "may not be evident until babies born by the Steptoe-Edwards method reach maturity." No woman should have wanted a baby under these stated conditions, nor should a (tax exempt) American Foundation have funded the Steptoe-Edwards trials, nor should any such thing ever



ever be approved by the Ethical Advisory Board. Only an unexamined preference for human design over nature can support any other conclusion.

No answer to the foregoing objection can be found in more time for trying in vitro fertilization in the sub-human primates, or the proposal that medical and public policy be to delay permission for applying this procedure to human beings until more "animal work" has been done. In other connections--when scientists need normal volunteers to place themselves at risk--the stress is always correctly placed on the unknown risk involved in moving from animals to the human.

In a 1974 scientific article one member of the winning team, Dr. Robert G. Edwards<sup>8</sup> of Cambridge University, asserted, "If there is no undue risk of deformity additional to those of natural conception, and publicity is avoided, the children should grow up and develop normally and be no more misfits than other children born today after some form of medical help." Here Edwards raised two points: how we are to estimate "undue" additional risks of deformity (whether any

such risks should be imposed) and the psychological damage that may result because publicity was not avoided in the case of Louise Brown.

On the first point, Dr. Edwards argues for 15 pages that there is no risk of deformity from the procedure. I understand why the risks are very low. The developing life (the blastocyst, not yet called an embryo) that is manipulated is a cluster of cleaving cells. These cells have "toti-potency." None is as yet on its way to becoming, say, blood, or has "clicked-off" its potency for becoming, say, a liver cell or a bone. At this point in human development the individual can renew itself even if momentarily injured (like an earthworm). After differentiation into various tissues and organs, the embryo and fetus is more vulnerable to irreversible damage. For example, by thalidomide taken by the mother during pregnancy.

Still there is risk of procedurally induced injury, however small. The question of "undue" additional risk remains at the heart of the moral question whether human genesis should ever be attempted in this way. Having carefully built the case for no undue risk, Dr. Edwards--to my amazement--then spends four pages warning all participants in this procedure that they are liable to "wrongful life" suits for tort compensation. As defendants, all the participants would have to prove that any manifest damage did not result from manipulating the blastocyst.

I was stunned by this contradiction in a single article by an eminent scientist because I heretofore supposed that only theologians were reputed to "fudge" in their arguments. In any case, knowing that one may induce injury, thought not foreseen injury, cannot be excluded. This seems to me to be significant in a conclusive moral argument against the experiments that have gone on for more than a decade. Moreover, even if longitudinal studies of in vitro children for the next five or ten years determines that they are in every respect normal, this will prove only that this kind of human genesis is at that point in time and for the future not to be condemned for this reason. Such success will not show that all the past trials at irremovable possible risk (including Louise Brown's) were for that period of time excusable. Two decades of morally unacceptable human experimentation, by

rough reckoning: one decade to perfect the technology; another to prove it was safe.

I once expressed the "macabre 'hope'" that the first child by laboratory fertilization would prove to be a bad result-- and that it be well advertised, not hidden from view. That might halt the practice! Dr. Edwards missed my irony, failing to note what else I said: "I do not actually believe that the good to come from public revulsion in such an event would justify the impairment of that child. But then for the same reasons, neither is the manipulation of embryos a procedure that can possibly be morally justified"--even if the result happens to be a Mahalia Jackson.<sup>9</sup> A small risk of grave induced injury is still a morally unacceptable risk.

Concerning the second source of possible grave damage-- publicity--I do not know whether or why Dr. Edwards changed his mind. Perhaps there was only a breakdown of communication between him and Dr. Steptoe, the gynecologist who advised that the next Brown be capitalized from birth. "Checkbook publicity," the British press calls it. One can speculate, however, as follows concerning the dilemma the winning team faced. They needed to prove their accomplishment to the scientific community and to the world at large. Already a British doctor had announced that there were one or more babies already born in Europe by this procedure. He offered



no proof, and was disbelieved. Nobody wins a Nobel prize for science that way.

If the Steptoe-Edwards team wanted both to advance science and/or their scientific reputations and to protect the next Brown from damaging publicity, they should have tried to create a new "institution" for doing both. The British Medical Association could have been asked to appoint a monitor who could now certify the team's achievement while at the same time avoiding publicity focused upon the subjects (the Browns) with whom the scientist-physician team have achieved their success.

In the absence of this anticipatory solution, there was no other recourse than to try to control the publicity and to enable Louise Brown to garner the revenues. She will be hailed or stigmatized all her life as the first laboratory fertilized progeny to be birthed in all human history. Think of the enormity of that reputation! "Brown" is an ordinary name; the father is a railway worker. Louise Brown can in no way have a natural human life. If she is not psychologically damaged from her beginning, socio-psychological ruin seems invited. If she is Britain's best tennis player at Wimbledon or if she becomes a juvenile delinquent, the outcome will be explained or excused by the child's unique genesis. Mahalia Jackson had a more obscure and normal passage into maturity. So also did the parents Brown, and Drs. Steptoe and Edwards. What now have they visited upon this child?

Perhaps Dr. Edwards' warnings about "wrongful life" suits could be taken up, and used to advantage. Such suits, (for having been born illegitimate, or in poverty) have not succeeded in American courts. Judges have reasoned that the plaintiff would not be there to sue if he or she had never been born. The plaintiff can have no legal standing to sue, because that depends upon the wrongful life he complains of. This seems to me to be the sound legal decision.<sup>10</sup>

In vitro fertilization and embryo manipulation, however, introduce quite different considerations. This form of human genesis reaches back to before the beginning. If tort damage results, there were human agents who did it--knowing the possibility could not be excluded. They should be liable. I do not say liable to punishment or to pay damages; but liable to suits that will determine their accountability. It can, therefore be recommended that our several State legislatures create a special category of "wrongful life" cases limited to torts occurring in this, and coming, new forms of human genesis. Then perhaps the practice can be stopped while there is still time.

### III

Among the parties liable and warned by Dr. Edwards in his 1974 article<sup>11</sup> was the "semen donor," not only the husband.

This demonstrates that one member of the winning team does not intend the procedure to be used only to the good end of overcoming a married woman's oviduct blockage.<sup>12</sup> This brings me to my third point, which brings into view the immediate and not unintended assault this procedure brings against marriage and the family, the immediate (not remote) possibility of the exploitation of women as surrogate mothers with wombs-for-hire, and the immediate (not remote and not unintended) spectre that we are going right now to begin to "design" our descendants up to the limit that is scientifically possible.

We are told that this sort of "assisted pregnancy" is a "far cry" from Aldous Huxley's Brave New World. This is true for the moment. Women with fallopian tube blockage now will be able with their husbands to have children. That is all.

Still there is more to be said about medical and public policy than that a woman's infertility can be "cured." This medical technology is another "long step for mankind" (to quote from the moon landing) toward Aldous Huxley's womb-free paradise. Host "mothers" with wombs-for-hire are immediately possible. Nothing technically limits the fertilization to the husband's sperm. We already have sperm banks. Egg banks will be next. People will go to either to select. No loved-woman need bear the child. This can be arranged by contract, and financial payment. The consequences to

come from the opening of the human uterus to medical technological control are not likely to contribute to the emancipation of women.<sup>13</sup>

There is still more. We are not limited to human progeny growing with their own natural genetic endowments. We are not limited to the child the Browns wanted. Gene splicing soon can be done before the blastocyst or embryo is transferred to the womb of the woman--any woman. "The procedures leading to replacement and implantation, Edwards and D.J. Sharpe wrote in a 1971 scientific article,<sup>14</sup> "open the way to further work on human embryos in the laboratory." The authors do not mean only benign attempts to correct genetic defects. They also mention cloning and the creation of "chimeras" by importing cells from other blastocysts (perhaps from other species). These creations also now need women to carry them through pregnancy. Noting that the first principle of medical ethics, "Do no harm", permits the alleviation of infertility, and that this "has been stretched to cover destruction of fetuses with hereditary defects, " Edwards and Sharpe ask rhetorically whether the first principle of medical ethics can be stretched to justify "the more remote techniques of modifying embryos?"

Even more ominous is the announced claim that scientists have the "right" to "exercise their professional activities



to the limit that is tolerable by society...as lay attitudes struggle to catch up with what scientists can do." Publics must be "helped to keep pace." In short, science does not operate within the ethics of a wider human community. It is a scientific ethics, or whatever can be done, that should shape our public philosophy. Let laggards beware.

True, in his 1974 article,<sup>15</sup> Dr. Edwards stated that there is "hardly any point in making chimeras until some clinical advantage can be shown to accrue from the method." But he also speaks of "sexing blastocysts" before transfer. His remedy for the problems this will lead to is: "Imbalance of the sexes could probably be prevented by recording the sex of newborn children, and adjusting the choice open to parents." Scientist-kings will manage everything. Concerning the use of "surrogate mothers," his only reservation is that this should be avoided at the present time until more is known about the interlocking psychological relationships among the parties. Edwards does not say how we can acquire such knowledge without (on his own terms) doing unethical experimentation now in order to find out whether we ought to do it or not.

#### IV

I have not yet mentioned the remote--but still very near--prospect of substituting laboratory generation from first to last for human procreation.

Pope Pius XII once warned against reducing the cohabitation of married persons to the transmission of germ life. This would, he said, "convert the domestic hearth, sanctuary of the family, into nothing more than a biological laboratory."<sup>16</sup> That quaint language was spoken about artificial insemination. The Pontiff feared the nemesis of humanity under the flourescent light of laboratories. He warned of this in 1951--ages ago in technological time. To the flurescent light of the laboratory has been added the glare of media protection and copy-righted publicity.

The first book to be printed entitled Test Tube Babies was published in 1934<sup>17</sup>--again ages ago in technological time. Its subject matter was not at all what we mean by this expression. The book's subtitle was "A History of the Artificial Impregnation of Human Beings, Including a Detailed Account of its Technique, together with Personal Experiences, Clinical Cases, A Review of its Literature, and the Medical and Legal Aspects Involved."

Clearly ours is an age of galloping biomedical technology. Aldous Huxley and C.S. Lewis had the prescience to see already the future that comes ever closer. Not the abuse of political power by Hitler nor of nuclear power but the unchecked employment of powers the biological revolution places in human hands was for these authors the final threat to the "abolition

of man."

The human womb is a half-way technology. It is replaceable by more "perfect" artifices.<sup>18</sup> Human life has been maintained in petrie dishes for two weeks; and our National Commission for the Protection of Human Subjects used 20-24 weeks as its definition of a "possibly viable" infant. Only about 18 to 22 weeks remain to be conquered in which the human female must necessarily participate in procreation, except as the source of the ovum. Then "reproduction" can replace procreation, and we will come to Huxley's Hatcheries. His was a vision of society in which everyone was quite happy. The way there is also a happy one, and we go along that way always motivated by good ends, such as the relief of women's infertility and salvaging "premies" earlier and earlier.

For all the motherhood intended at present, the truth is that (as C.S. Lewis once wrote<sup>19</sup>): "We should not do to minerals and vegetables what modern science threatens to do to man himself."

Members of the Ethical Advisory Board may wish to perform the following experiment on themselves. Turn off the tube. Don't pick up the newspaper for two days. Instead, read the third of C.S. Lewis' space-science trilogy, That Hideous Strength. The final assault upon

humanity is gathering in Edgestow, a fictional British college town. The forces of technology, limited no more by the Christian ages, are trying to combine with pre-Christian forces, represented by Merlin the Magician whose body is buried on the Bracton College grounds. Only the philologist Ransom can save humankind from the powers of the present age concentrated in the National Institute for Coordinated Experimentation (acronym NICE).

It is NICE that the Browns have a wonderful baby girl; her middle name is Joy. Lewis need not have thought of his fictional college, Bracton. Cambridge University is NICE too. So is Vanderbilt. To give couples a baby sexed to their desires will be NICE. Every other step taken will certainly be NICE. Finally, Brave New World is entirely NICE. For everyone is happy in Huxley's pharmacological, genetic and womb-free paradise. Only there is no poetry there. Nor does a baby have the right to be a surprise.



FOOTNOTES

1. "Shall We 'Reproduce'?" JAMA, Vol. 220, Nos. 10 and 11 (June 5 and 12, 1972), pp. 1346-1350 and 1480-1485.

2. In addition to numerous articles, the titles of four volumes perhaps deserve mention (all published by the Yale University Press): The Patient as Person: Explorations of Medical Ethics. The Lyman Beecher Lectures delivered at Yale Medical and Divinity Schools (1970); Fabricated Man: The Ethics of Genetic Control (1970); The Ethics of Fetal Research (1975); and Ethics at the Edges of Life: Medical and Legal Intersections. The Bampton Lectures in America, Columbia University (1978).

3. Beal v. Doe, no. 75-554, 45 LW, pp. 4781-87; Maher v. Roe, no. 75-1440, 45 LW, pp. 4787-94; Poelker v. Doe, no. 75-442, 45 LW, pp. 4794-97 (the three decisions handed down June 21, 1977).

4. See my Ethics at the Edges of Life, op. cit., Chapter Two.

5. Joseph M. Boyle, Jr., and Germain Grisez, unpublished manuscript with "model bill" and commentary.

6. Henry Nadler, M.D. in Maureen Harris, ed.: Early Diagnosis of Human Genetic Defects. Washington, D.C.: U.S. Government Printing Office, 1972. Pp. 315, 230.

7. Walter Sullivan, "Successful Laboratory Conception Intensifies Debate over Procedures," The New York Times, July 27, 1978.

8. R.G. Edwards, "Fertilization of Human Eggs in Vitro: Morals, Ethics and the Law." The Quarterly Review of Biology, 49:1 (March 1974), pp. 3-26. (Stoney Brook Foundation, Inc.) Italics added.

9. Paul Ramsey, "Shall We Reproduce?", Journal of the American Medical Association, 220:11 (June 12, 1972), p. 1482. My suggestion paraphrased and reversed a statement by Dr. Joshua Lederberg concerning whether "cloning" human beings will be socially acceptable. This depends, he wrote, on the first clonant's batting average; and on his good looks, success and being well advertised. Joshua Lederberg, "Experimental Genetics and Human Evolution," The American Naturalist, Vol. 100 (Sept.-Oct., 1966), pp. 519-31; slightly revised and reprinted. Bulletin of Atomic Scientists, Oct., 1966, pp. 4-11. See also my Fabricated Man, op. cit., Chapter Two.

10. A convenient reference for those decisions, with commentary, is Joel Feinberg, ed., The Problem of Abortion. Belmont, California: Wadsworth Publishing Company, 1973.

11. See note 8 above.

12. Testifying before the Sub-Committee on Health and the Environment, U.S. House of Representatives, on August 4, 1978, Dr. James C. Gaither, Chairman of the Ethics Advisory Board, offered the opinion not only that implantation of human fertilized ova should not be done until the safety of the procedure is demonstrated as far as possible in subhuman primates. He also testified that it was the opinion of some 20 experts in ethics and the life sciences convened by DHEW that such a procedure should await definition of the responsibilities of the donor, recipient "parents," and of the research institution. Walter J. Wadlington, professor of law at the University of Virginia Law School, urged that Congress propose model legislation for use by the States in coping with such problems as legitimacy and parental responsibility if in vitro fertilization becomes widespread. The New York Times, August 5, 1978.

13. Here I quote from a striking letter to The New York Times (August 6, 1978) by Judith Lorber, Department of Sociology, Brooklyn College:

"I am thankful that the first child born from laboratory fertilization is a girl. At least now there are two female principals in the drama, instead of one lonely woman surrounded by powerful and prestigious male doctors,

male scientists, male legal, ethical and religious experts, male newspapermen, and so on and on.

"Men now have the ability to freeze their sperm, fertilize eggs in vitro and deliver the children surgically, and the potential ability for freezing embryos and transplanting them in women other than the egg producers. Fortunately, a woman's body is still needed to carry the fetus to term.

"But women of the future had better get more than a toehold in the bastions of power. Otherwise, when male-dominated technological reproduction develops artificial wombs, too, women, except for a select few egg producers, may end up totally superfluous."

14. R.G. Edwards and D.J. Sharpe, "Social Values and Research in Human Embryology." Nature 231: 87-91 (1971). Italics added.

15. See note 8. above.

16. Acta Apostolicae Sedis 43:850 (1951).

17. Dr. Hermann Rohleder, Test Tube Babies. New York: The Panurge Press, 1934. Can we use "panurge" as a symbol for the basic problem of modern times, since Bacon unfurled the flag for "the relief of the human estate" of disease, suffering, death, and any other deficit?



18. If I were a reproductive biologist in need of funds and reputation, and anyway a sincere believer in progress by science, I would begin now to search for an animal species whose gestation is close enough to the human for it to be not impossible to use its females as hosts for human embryos. After all, "herds" of prime cattle in embryo have been flown across the Atlantic within rabbits, thereafter to be transferred again to scrub cows to bear them. So my idea is not a fanciful one (if we ought to treat the human embryo like cattle). If I can secure funds for my trials I may gain Senator Proxmire's "golden fleece" award, even if I do not gain an honored place in the moral history of humankind.

19. C.S. Lewis, The Abolition of Man. New York: MacMillian Co., 1947.



## II

### SCIENTIFIC ISSUES





IN VITRO FERTILIZATION, EMBRYO CULTURE AND  
EMBRYO TRANSFER IN THE HUMAN

John D. Biggers, D.Sc., Ph.D.



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## INTRODUCTION

The possibility of giving women, who are infertile because of non-functional, destroyed or absent oviducts, the opportunity to have a child by in vitro fertilization, ovum culture and transfer was first mentioned by Shettles (1955). Later, at a meeting of the New York Obstetrical Society held November 12, 1957, Dr. John Rock of Harvard Medical School, when discussing another paper by Shettles, commented:

" The time may be rapidly approaching when the poor woman whose tubes have been excised, yet who still wants a baby, will rejoice that Dr. Shettles will be able to extract an ovum from her ovary, probably not by laparotomy, but through an operating telescope (which can be done - we have done it); then fertilize the egg in vitro by the husband's spermatozoa; and finally put it back in the uterus. Thus, he will impregnate the woman in spite of the fact she has no tubes".

Rock's prophetic prediction preceded that of Edwards by about 8 years (Edwards, 1965) and its realization by 21 years. Nevertheless, we should recognize that it was the perserverance of Edwards and Steptoe that brought John Rock's scenario to reality last July by the birth of Louise Brown (Steptoe and Edwards, 1978).

The primary achievement of Edwards and Steptoe was to develop by 1971 a technique for the fertilization of human follicular oocytes in vitro, thereby providing a potential supply of human preimplantation embryos for

fundamental and clinical investigations. Of no less importance, Edwards and Steptoe have developed a method for transferring a human preimplantation embryo produced by in vitro fertilization into the uterus of the donor of the oocyte so that the embryo can develop into a full-term fetus capable of life after birth. Whether society should support the production of human preimplantation embryos for fundamental research or treatment of infertility clearly invokes ethical questions. I am honored by the invitation to present a background review of the scientific and technical details of the area to help the Ethics Advisory Board, Department of Health, Education and Welfare, in their analysis of the ethical questions involved, and in deciding whether the moratorium imposed in 1975 should be discontinued.

Between 1970 and 1975, several investigators in the United States were involved in the study of in vitro fertilization of human ova (Jacobson, Sites and Arias-Bernal, 1970; Mastroianni and Noriega, 1970; Brackett, Seitz and Mastroianni, 1971; Seitz, Rocha, Brackett and Mastroianni, 1971; Soupart and Strong, 1974). At present, I know of only four laboratories overseas who are working on the in vitro fertilization of human ova. These are Edwards and Steptoe, a group at the Universities of Melbourne and Monash in Australia (Lopata et al., 1978), a group at the Institute of Obstetrics and Gynecology, USSR Academy of Medicine, Leningrad (Petrov-Maslakov et al., 1973), and a group at the University of Hamburg (Castenen et al., 1977). It is likely there are more.

I believe it is essential for Members of the Board to recognize a golden rule that the results of all studies in vitro should be evaluated in terms of the normal events in the intact organism. For this reason, I discuss at length the reproductive processes during early pregnancy in women.

I also believe that it is important for the Members of the Board to

appreciate that the achievements of Edwards and Steptoe rested on the techniques and the complex interaction of ideas contributed by many scientists, some using human material. This fact is not surprising for technological advances at any given time depend jointly on the available body of scientific knowledge and its contemporary interpretation. I have therefore used the historical approach in my assessment of Edwards and Steptoe's work, for, in the words of Cicero:

"Not to know what took place before you were born is  
to remain forever a child".

Some of the relevant research was in fact done before any of us were born.

## ESTABLISHMENT OF PREGNANCY

### The System

A primary function of the reproductive process in all organisms is the generation of genetic variability. This involves creating in each individual a new sample of the gene pool. The information carried by this sample of genes determines in part the developmental history of the individual from the time it is created until it dies. It has been estimated that there are approximately 30,000 genes in each sample in the human (United Nations, 1972); each member is a representative of several candidates called alleles that exist in the gene pool. Thus, the opportunity for variation is enormous, and the probability of any two individuals being genetically the same is almost zero - hence the uniqueness of the individual. The continual production of new unique individuals by a species allows that particular species to adapt to the slow inexorable changes that occur in the universe in which we live.

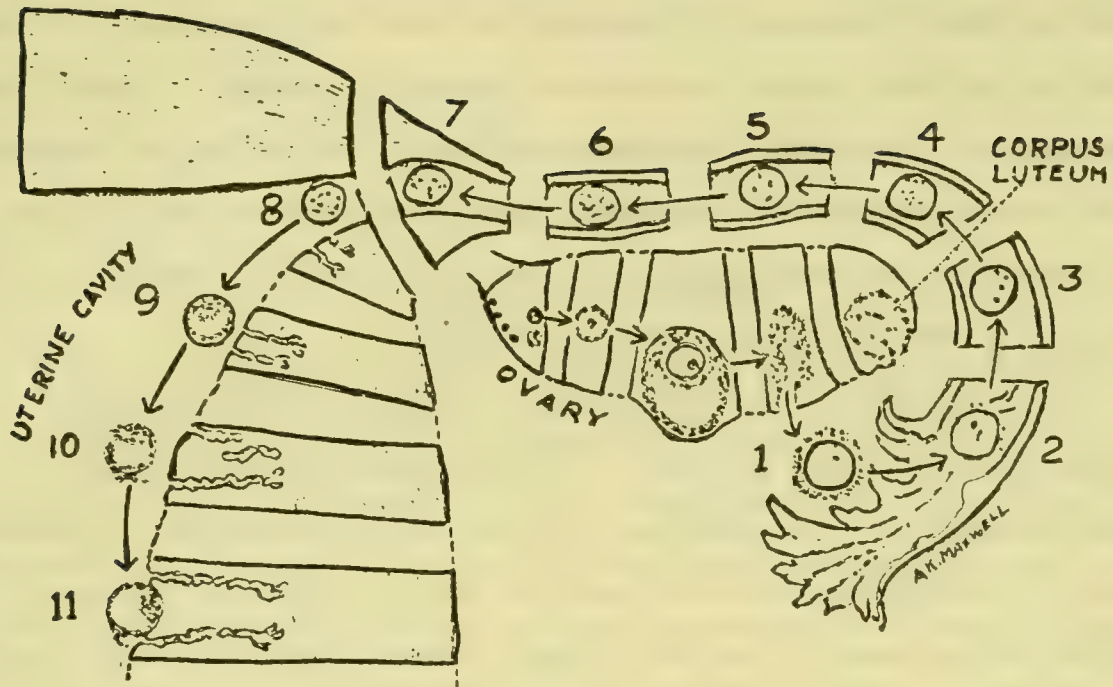
The reproductive mechanisms of human beings, like all mammals, are

specialized, and are characterized by using the processes of meiosis and fertilization to produce the variation just described. The mechanisms are further specialized for the nurture of the young during development by the processes of internal fertilization and viviparity - the bearing of live young.

Figure 1 illustrates the processes involved in the establishment of pregnancy in a woman. At approximately midtime between two menstrual periods, an ovum is released either from the left or right ovary into the upper region of the oviduct. This part of the oviduct is called the ampulla. If coitus occurs at this time, sperm are deposited in the vagina and a few of them are transported up the female tract through the cervix, uterus and lower oviduct to the ampullary region. An encounter between a sperm and ovum in the ampullary region frequently results in their fusion - the process called fertilization. The single cell that results from the fusion of a sperm and ovum is called a zygote, and it contains all the genetic information necessary to determine the life of a new individual. Thereafter, the zygote undergoes a series of cell divisions, called the cleavage divisions, to produce a ball of cells called a morula. Eventually the outer cells of the morula become closely associated to form the first tissue in the embryo - the trophectoderm. The trophectoderm forms an outer skin whose function controls the formation and composition of the fluid within the embryo. The development of this capability provides the mechanism for the accumulation of fluid in the embryo so that it forms a cystic structure - the blastocyst. At this stage, the blastocyst consists of three parts - the outer trophectoderm, a collection of internal cells located in one area, - the inner cell mass and the blastocoele fluid. The trophectoderm will subsequently interact with the cells lining the uterus to form the placenta.



Figure 1. (Hamilton, Boyd and Mossman, 1945)



A schematic representation of the development of the ovarian follicle, its growth, maturation and rupture. The passage of the ovum into the tube and its fertilization, subsequent development and implantation are depicted. (Based on Dickinson.) (1) Unsegmented oocyte at the 2nd maturation spindle. (2) Fertilization. (3) Eccentrically placed pronuclei and polar bodies. (4) 1st spindle of division. (5) Two cell stage. (6) Four cell stage. (7) Eight cell stage. (8) Morula. (9) and (10) Free Blastocyst in uterine cavity. (11) Early phase of implantation.

This interaction is called implantation. The cells of the inner cell mass will eventually develop into the tissue and organ systems of the embryo. At the the beginning of implantation, the embryo is "free living" within the genital tract of the mother in the sense that it is not anchored to the mother's tract but floats freely in the fluid secretions. During this time the embryo migrates from the ampullary region of the oviduct, through the lower isthmus region, to the uterus - the tubal journey. The period of development between fertilization and implantation is called the preimplantation stages of pregnancy. Note that several important processes occur while the ovum and embryo are free in the genital tract - fertilization, cleavage, blastocyst formation and implantation.

Our knowledge of the initial stages of human development is very limited (Biggers, 1978; Appendix 1). Measurements of the size of the human ovum show that in comparison with many other species, it is a large type. Our information on preimplantation ova and embryos is confined only to 15 specimens, a very small sample. Nevertheless, the data suggest that the tubal journey in women takes about 3 days, and that the embryo enters the uterus as an early morula. Implantation occurs approximately 6 days after fertilization.

#### Two caveats on terminology

The birth of Louise Brown was possible because fertilization of an ovum from her mother by a sperm from her father, and her early preimplantation development was accomplished in vitro independently of her mother, prior to the successful transfer of her back into her mother's uterus shortly before implantation. The popular description of Edwards' and Step-toe's total achievement as "in vitro fertilization" places emphasis on only

a restricted aspect of the mechanisms involved in ensuring that life never stops between generations. As I pointed out in testimony to the U.S. Senate Subcommittee on Constitutional Amendments of the Senate Judiciary Committee on May 7, 1974 (Appendix 2), an excessive concern with fertilization may be inappropriate in analyzing ethical questions.

Pregnancy in women lasts on average 267 days with a standard deviation of 10 days. Thus, the preimplantation period lasts for only the first 2.25 percent of the total duration of pregnancy. I suggest, therefore, that the emotive phrase 'test-tube baby' be eliminated from our discussion.

#### Performance of the System

Recently, Roberts and Lowe (1975) wrote an article in the Lancet with the intriguing title "Where have all the conceptions gone?". Their analysis which I will return to later, showed that a very high rate of embryonic loss occurs in women during the normal reproductive process. Their article was of course pointing out that a phenomenon well known in non-primates exists in our own species. That embryonic death is a normal process in mammalian reproduction was first suggested by Hammond (1914) from his studies on pigs. The widespread occurrence of this phenomenon was pointed out again by Robinson (1921) under interesting circumstances. Robinson was honored with the invitation to give the Sir John Struthers Lecture of the Royal College of Surgeons of Edinburgh which was established with the stipulation that the lecturer should not discuss problems in pathology. Robinson, who wanted to discuss embryonic death, cleverly avoided the restriction in Struthers' will by arguing that although the death of a particular embryo involves pathological processes, embryonic death is so widespread in mammals that it should be accepted as a normal phenomenon. Corner (1923) also reached the same conclusion.

The magnitude of embryonic death has been studied extensively in domestic animals (Table 1). In some species it is very high, such as in the pig where a normally fertile animal may lose as many as 40 percent of her embryos in each pregnancy. Examples of extreme ovum and embryonic loss are also known. For example, the plains viscacha (a rodent from South America related to the guinea pig), ovulates up to 800 ova at once, seven are fertilized but only two embryos are born (Weir, 1971).

So far the discussion has been concerned with embryonic death in polytocus species- animals producing more than one young per pregnancy. The effect of partial embryonic death in these species is to reduce litter size and not reduce the incidence of pregnancies. In contrast, in a monotocus species producing a single offspring per pregnancy, such as the human, the effect of embryonic death is to eliminate the pregnancy.

The fact that embryonic loss occurs in women was first recognized by Hertig and Rock (1949), who recovered several potentially abortive ova from women considered to be normally fertile. Only recently has it been recognized that this embryo loss may be high. Leridon (1973) used the updated data of Hertig et al. (1959) on the incidence of blighted human embryos obtained in Boston together with the data on fetal mortality obtained in a study on the island of Kauai during 1953-1956 inclusive (French and Bierman, 1962), to construct a life-table for intra-uterine mortality throughout pregnancy (Table 2). The results show that 69 percent of human ova exposed to spermatozoa are lost by the expected time of birth. The table also shows a large incidence of failure of fertilization (16 percent),



Table 1. From Biggers, 1969.

INCIDENCE OF EMBRYONIC MORTALITY IN NORMALLY FERTILE CATTLE, PIGS, AND SHEEP

Species	Day examined	Embryonic mortality (%)	Reference
Cow	33	14.9	Bearden, Hansel & Bratton (1956)
Cow	90	16	Kidder, Black, Wiltbank, Ulberg & Casida (1954)
Cow	150	19.9	Hawk, Tyler, Casida (1955)
Cow	100	20.6	Erb & Holtz (1958)
Cow	27	21	Laing (1949)
Pig	55	23	Reddy, Moyer & Lasley (1958)
Pig	25	30-43	Baker, Self, Chapman, Grummer & Casida (1956)
			Baker, Chapman, Grummer & Casida (1958)
Pig	25	33	Day, Anderson, Emmerson, Hazel & Melander (1959)
Pig	25	34	Lerner, Mayer & Lasley (1957)
Pig	25-40	34.8	Perry & Rowlands (1962)
Pig	28	39	King & Young (1957)
Pig	term*	40	Perry (1954)
Pig	term	41	Lasley (1957)
Pig	term	44	Casida (1953)
Pig	70	50	Baker, Self, Chapman, Grummer & Casida (1956)
Sheep	40	30	Hulet, Voigtlander, Pope & Casida (1956)

\*75% of the embryos died by the 25th day.

Table 2

A life-table for intra-uterine mortality in the human  
(per 100 ova exposed to risk of fertilization) (from  
Leridon, 1973).

<u>Weeks after</u> <u>Ovulation</u>	<u>Deaths</u>	<u>Survivors</u>
	16*	100
0	15	84
1	27	69
2	5	42
6	2.9	37
10	1.7	34.1
14	0.5	32.4
18	0.3	31.9
22	0.1	31.6
26	0.1	31.5
30	0.1	31.4
34	0.1	31.3
38	0.2	31.2
Number born		31

\* Failure of fertilization

and a large incidence of embryo loss during the first two weeks of pregnancy. The combination of data concerning the early embryonic wastage observed in the Boston Hospital for Women with a public health survey on the outcome of pregnancy in a Pacific Island may cause skepticism over the homogeneity of the data, and therefore concern about the conclusions. However, other series of independent evidence support the conclusion that high embryonic loss occurs in the human. Roberts and Lowe (1975), using statistics based on reproductive performance, estimated that 78 percent of embryos are lost, a slightly higher percentage than that estimated by Leridon (1973). An estimate between 69 and 78 percent embryonic loss, however, is reasonably consistent with data showing that it takes an average of four months of regular inseminations to achieve pregnancy by artificial insemination.\* Thus, it may take an average of four months of continuous sexual activity to establish a pregnancy capable of producing a normal full-term baby (MacLeod and Gold, 1953).

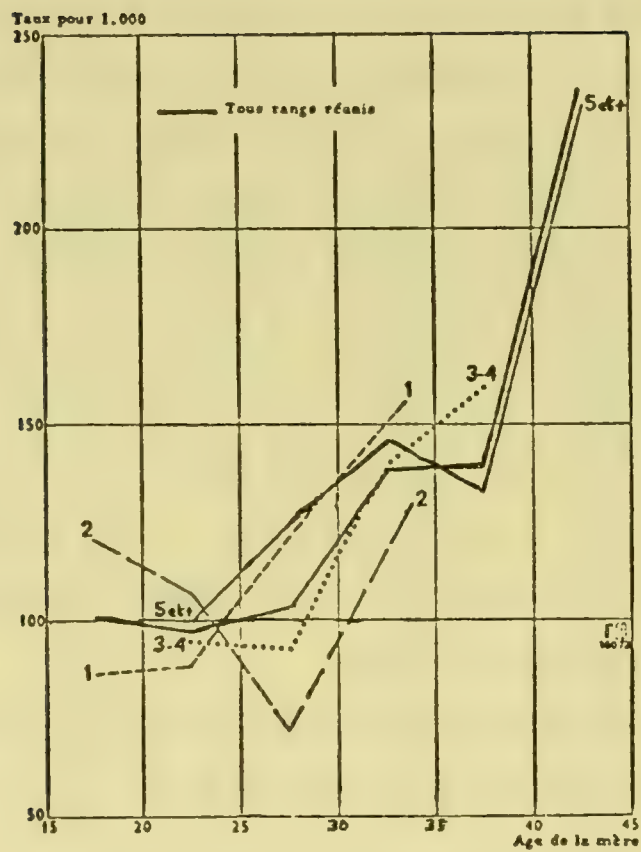
Embryonic loss also increases significantly with the age of the mother, particularly after the age of 35 years (Fig. 2).

#### Causes of embryonic loss

The death of an embryo may arise from two primary causes. One cause originates in the intrinsic abnormalities in the embryo that are lethal, such as unmasked recessive genes and chromosomal aberrations. The other cause originates in lethal environmental effects mediated via the female genital tract. These effects may be due to normal ageing processes in the female tract (Biggers, 1969), disease of the genital tract, or the transmission of exogenous teratogenic agents. Studies of the incidence of

\* Chong and Taymor, 1975; data from Boston Hospital for Women

Figure 2. From Leridon, 1973



Mortalité intra-utérine selon l'âge de la mère  
et le rang de la grossesse. (Martinique).



cytogenetic aberrations in spontaneous human abortions show that a major factor in embryonic loss is chromosomal imbalance that arises during the maturation of the oocytes and spermatozoa, and during fertilization.

Boué and Boué (1976) argue that chromosomal aberrations that arise during gametogenesis and fertilization account for a loss of 50 percent of human embryos that are potentially existent at the time of fertilization. The cause of the 25 percent deficit in embryonic loss between the estimates of Leridon (1973) and Roberts and Lowe (1975), and Boué and Boué (1976) is presumably due to unmasked recessive genes and environmental factors of non-genetic origin. The contribution of these three factors is unknown. Much more is known about the cytogenetic factors involved in the loss of human embryos than the other factors.

#### Meiosis, fertilization and the origin of cytogenetic aberrations

Each human being possesses 23 pairs of chromosomes; one member of each pair is derived from the person's father and the other member from the mother. Thus, we speak of the haploid set ( $\underline{n} = 23$ ) of paternally derived chromosomes and the haploid set ( $\underline{n} = 23$ ) of maternally derived chromosomes. At fertilization, the sperm cell carries a paternal haploid set into the ovum to become associated with a maternal haploid set. The joint haploid sets form the diploid set ( $2\underline{n} = 46$ ) of chromosomes that are characteristic of the adult. Each haploid set consists of 22 autosomes and one sex chromosome. There are two types of sex chromosomes denoted X and Y. A human female has 2X chromosomes, one derived from her father. A human male has an X chromosome derived from his mother and a Y chromosome derived from his father. Thus, it is the male that determines the genetic sex of the offspring depending on whether the

ovum was fertilized by an X-bearing or Y-bearing sperm. The autosomes, numbered 1-22 inclusive, are divided into several groups denoted by the letters A through G.

Ova and sperm are developed in the ovary and testis, respectively, by a process called gametogenesis. Chromosome maturation is produced in both sexes by a process called meiosis. This process consists of two special cell divisions in which the chromosome number is reduced from the diploid to the haploid set. Thus, it is the separation of X and Y sex chromosomes in the male during meiosis that leads to the two types of sperm cells.

During meiosis, several accidents may occur resulting in sperm and ova with abnormal numbers of chromosomes. For example, the sex chromosomes may not separate, resulting in sperm that contain both X and Y chromosomes or no sex chromosomes, or ova containing two X chromosomes or no sex chromosomes. In the same way, any of the 22 pairs of autosomes may fail to separate. This type of aberration is called non-disjunction. Estimates of the incidence of non-disjunction of chromosomes 1, 9 and Y in human spermatozoa have been found to be 3.5, 5 and 2 percent, respectively (Pearson, Geraedts and Pawlowitzki, 1963). These are considered high rates. Fertilization involving any of these abnormal sperm or ova can result in abnormal embryos. For example, if a normal ovum is fertilized by a sperm without a sex chromosome, an XO embryo is produced who suffers from Turner's syndrome. Such an individual has only 45 chromosomes, and is an example of a general class of aberration called monosomy. If an ovum with two X chromosomes is fertilized by a normal Y-bearing sperm, an XXY individual is produced who suffers from Klinefelter's syndrome. Such an individual has 47 chromosomes and is an example of a general class of aberration called trisomy. Non-disjunction of the G class of chromosomes

(#21,22) can result in trisomy G that causes Down's syndrome (mongolism).

Other types of accident can happen. Failure to complete meiosis may occur so that an ovum or sperm is produced which has the full diploid set of chromosomes. If, for example, a diploid ovum is fertilized by a normal sperm, a triploid embryo ( $n = 69$ ) is produced. Normally, only one sperm enters the ovum at fertilization. The entry of more than one sperm is prevented by the block to polyspermy. If this mechanism fails, one or more sperm may enter the ovum at fertilization, giving triploids, tetraploids, etc. The recent studies of Beatty (1978) and Jacobs et al. (1978) suggest that most human triploid embryos are formed naturally by dispermic fertilization as the result of failure of the block to polyspermy.

There is a significant absence of autosomal monosomies in spontaneous human abortions. Boué and Boué (1976) argue that these aberrations must be produced in numbers equivalent to the trisomies, but that they cause embryonic death so early that they cannot be detected. Their elimination may in fact occur before the first missed menstrual period. Studies of the phenomenon in the tobacco mouse by Gropp (1973) support this view.

#### Fate of cytogenetic aberrations

The presence of an abnormal number of chromosomes may or may not be lethal. For example, the XXY trisomy is compatible with post-natal life, the XO monosomy, as well as trisomy G, is predominantly lethal in fetal life but some are born. Triploidy, however, is nearly always lethal in embryonic life, and those that are born only survive postnatally for a short time. Studies on the chromosome complements in spontaneous abortions in women have provided information on when embryos with the different types of

chromosome aberration die (Fig. 3). Some types, such as tetraploidy ( $N = 92$ ), trisomy C and trisomy E, are on average, lethal a few weeks earlier than other types such as monosomy X, triploidy, trisomy D and trisomy G. Nevertheless, nearly all of them become developmentally arrested by the eighth week of pregnancy.

#### Maternal selection against malformed embryos

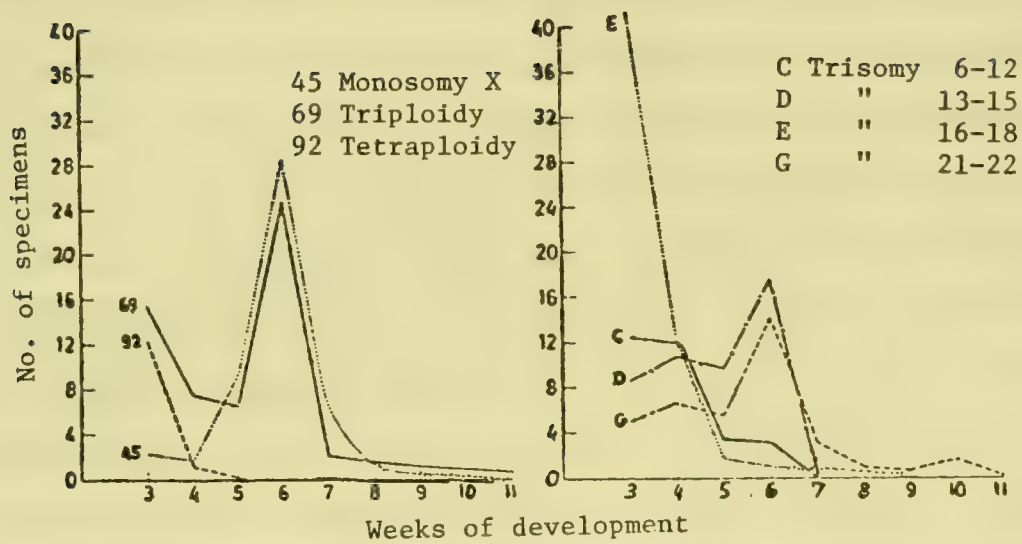
In all species, reproductive performance decreases with maternal age. In polytocous species, this decline is also associated with a decrease in the incidence of congenital abnormalities in the newborn (Parsons, 1963; Kalter, 1971). A recent study by Kalter (1978) on the incidence of cleft lip-palate and open eyelid in litters of A/JKt mice suggests that deformed embryos are more likely to die in utero in older females. This is the first evidence that advanced maternal age can lead to differential death of malformed fetuses. Parsons (1963) suggests the cause of selection is the competition between fetuses for the limited resources of the uterus. Such competition would not occur in a monotocous species like the human and this may be the reason why increase in the incidence of several congenital abnormalities, such as mongolism, central placenta praevia, malformations of the nervous system, and cleft lip and palate, occurs with advancing age.

#### Summary

There is strong evidence that there is a high incidence of embryonic death in the normal reproductive process in humans. A large component of this arises from errors in meiosis in the male and female, and in errors of fertilization such as failure of the block to polyspermy. Normally, most of the abnormal embryos die and are eliminated early in pregnancy. Nevertheless,



Figure 3. From Boué and Boué, 1976.



Developmental age (in weeks) of abortuses with different types of chromosomal anomalies: a. Monosomy X, triploidy and tetraploidy. b. Trisomies C,D,E, and G.

a few do not die and are eventually born as congenital abnormalities. The incidence of these abnormalities at birth increases with maternal age.

#### EARLY STUDIES ON *IN VITRO* FERTILIZATION AND EMBRYO TRANSFER

The entrance of a sperm into an egg was first reported 101 years ago by Fol in his studies on the starfish, a species where fertilization normally takes place after shedding the ova and sperm into the seawater. Our understanding of the genetic significance of this observation depended on the discovery just before the turn of the century, of the chromosomes and their behaviour, and the rediscovery of Mendel's work in 1900, which introduced the notion of particulate inheritance. Nevertheless, before this time, Schenk (1880) and Onanoff (1893) attempted to study the fusion in vitro of sperm and ova in rabbits and in guinea pigs although it is very doubtful that they were successful. Of greater interest is that in 1890, Walter Heape, working in Cambridge, England, successfully transferred two ova from an Angora doe rabbit, which had been fertilized by an Angora buck, into the oviduct of a Belgian hare doe rabbit, which had mated a few hours before. In due course, six young were born, of which two were undoubtedly Angoras. Heape undertook this experiment "to determine in the first place what effect, if any, a uterine foster-mother would have upon her foster-children, and whether or not the presence and development of foreign ova in the uterus of a mother would affect the offspring of that mother born at the same time". This experiment demonstrated neither effect and was confirmed by his further work published in 1897. Thus, in pursuing basic questions on the possibility of maternal influence and acquired inheritance, Heape demonstrated it is physiologically possible to recover a preimplantation stage embryo from a mother by flushing the oviduct, and then transfer it to a foster-mother

without interfering with development.

Embryologists were also keen to study living early mammalian embryos and attempts to culture them were made only five years after the first successful culture of nerve cells by Ross Harrison at Yale in 1907. Progress in the field was slow and despite attempts by several distinguished scientists - Warren Lewis, Pincus and M.C. Chang - it was not until 1949 that John Hammond, Jr., also working in Cambridge, England, found a complex medium that permitted 8-cell mouse embryos to develop into blastocysts. Later, Whitten (1956) showed that a complex medium was not needed and could be replaced by a simple chemically-defined medium. Soon after, McLaren and Biggers (1958) combined the technique of Whitten with the transfer technique first done by Heape, and showed that mouse embryos could be cultured from the 8-cell to blastocyst stage, and then be transferred to a uterine foster-mother, where they develop into normal young. Some of these offspring grew to adult mice and reproduced naturally to yield another generation. In this work, no abnormal offspring were found although it should be recognized that the scope of the experiment was limited in size.

Meanwhile, progress in achieving fertilization in vitro also moved slowly. Many attempts were made between 1930 and 1959 (see Austin and Walton, 1960, for a critical review). Among these studies were those of Rock and Menkin (1944) and Menkin and Rock (1948), who reported they exposed 138 human follicular oocytes to spermatozoa, and Shettles at Columbia, whose first attempt to fertilize human oocytes was reported in 1953. The problem with all of the early studies of in vitro fertilization in the human and non-human species was the failure of all investigators to use stringent criteria necessary to prove that fertilization actually occurred.

In 1959, M.C. Chang of the Worcester Foundation, Massachusetts, overcame these difficulties by combining the in vitro fertilization technique developed for the rabbit with Heape's transfer technique. In these experiments, the sperm were taken from males with specific genetic traits not present in the females donating the ova. The appearance of the male traits in the offspring provided unequivocal proof that genetic information was conveyed to the ova by the sperm from the male.

Thus, by 1960, the stage was set for the rapid expansion of several types of work, basic and applied, in the study and manipulation of mammalian embryos. The current areas of active research are many (Table 3).

#### DEVELOPMENT OF THE TECHNIQUE FOR USE IN WOMEN

##### Collection of Mature Ova

In most of the work with animals, unfertilized ova and early pre-implantation embryos can be recovered by flushing the oviduct at the appropriate times. These procedures cannot be done on women without destroying the oviduct. Thus, the early work on women focused on developing a technique for the recovery of oocytes from the ovary before fertilization. This approach also has the advantage of providing more ova at the same time for in vitro fertilization.

To understand this work, it is necessary to understand the physiological processes involved in the release of a mature ovum at the time of fertilization. Figure 4 shows the number of germ cells (oocytes) in the ovaries of the human female throughout her life. By the age of 6 months after fertilization, a fetal girl has produced about 7 million oocytes. These oocytes are all she will produce and this set is called the finite oocyte store. Thereafter, a large proportion of these cells die and disappear, so that at birth, a



girl is left with only 2 million oocytes, and at puberty only about 400,000. Then, once a month, unless she becomes pregnant, one of these oocytes is selected for ovulation. It is easy to calculate that if a woman ovulates a single ovum monthly from the age of 15 to 50 years inclusive without becoming pregnant, only 468 oocytes are selected for release from her ovaries. Yet a woman's ovaries at the end of menopause are devoid of oocytes. Thus, by the time the reproductive period of life ends, approximately 99.9 percent of potential ova present in the ovaries at puberty are discarded by the process of normal cell death. The large loss of oocytes in women, however, is miniscule compared to the loss of male gametes. A man differs from the woman in that he produces spermatozoa in large numbers throughout his reproductive life. There is no finite spermatozoa store. At each ejaculation, a man releases 200 million spermatozoa, 30 times more gametes than a woman ever produces in her life.

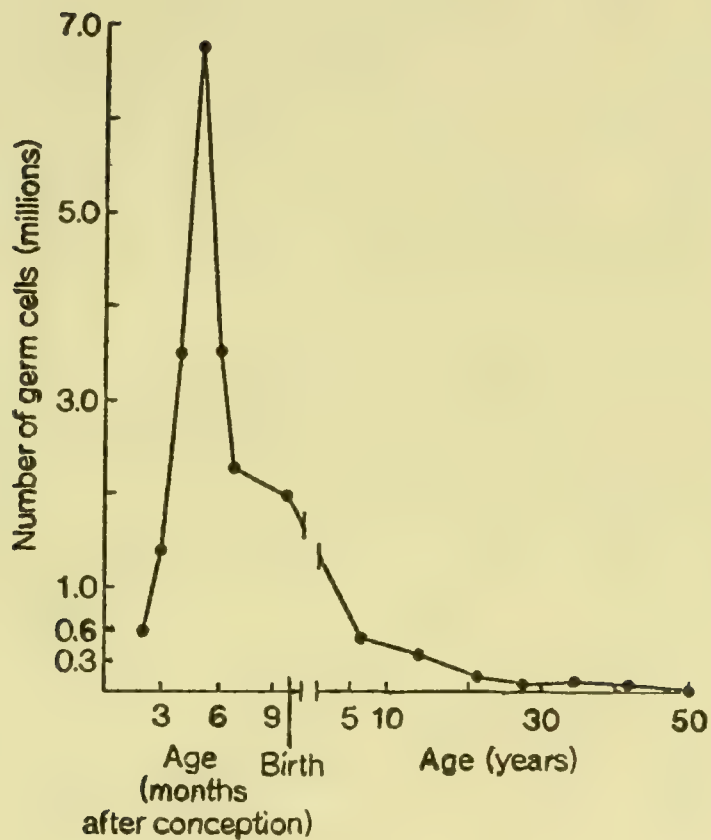
By the time of birth, all cells in the finite oocyte store have begun the process of meiosis. The process of meiosis in the human female, however, does not proceed continuously but is episodic in nature, with two periods of arrest requiring specific signals to proceed to the next stage. By the time a girl is born, all oocytes in the finite oocyte store have entered the first meiotic division and become arrested before completion of the division. The oocytes are said to be arrested in the diplotene stage of the first meiotic division. The oocytes will remain in the diplotene stage unless they are selected to be ovulated and perhaps die. Thus, an oocyte that is selected for ovulation in a 50 year old woman has stayed in the diplotene condition for just over 50 years. If the oocyte is selected to be ovulated, it matures by proceeding to the next stage of arrest. This occurs towards the end of the second meiotic division, and arrest occurs

Table 3

Areas of research involving in vitro  
fertilization, embryo culture and  
embryo transfer.

<u>Area</u>	<u>Recent Monographs and Reviews</u>
Experimental embryology	(Balls and Wild (1975) (McLaren (1976) (Sherman (1977) (Johnson (1977)
Physiology of preimplantation development	Biggers and Borland (1976)
Freezing and preservation of embryos	Ciba Foundation Symposium (1977)
Embryo transfer in domestic animals	Rowson (1975)
Fertilization	Yanagamachi (1977) Gwatkin (1977)
Oncology	Sherman and Solter (1975)

Figure 4. From Baker, 1972.



Changes in the total population of germ cells in the human ovary with increasing age. (From T. G. Baker, Radiosensitivity of mammalian oocytes with particular reference to the human female, *Amer. J. Obstet. Gynec.* 110, 746-61, Fig. 1 (1971); data for prenatal period derived from T. G. Baker, *Proc. Roy. Soc., Biol.* 158, 417 (1963); data for children and adults from E. Block, *Acta Anat.* 14, 108 (1952).)

at the metaphase II stage. In women, the passage from the diplotene stage to the metaphase II stage takes only about 36 hours. The factors that determine the selection of a particular member of the finite oocyte store for ovulation are unknown and its study is one of the challenging problems in the reproductive biology of mammals. However, it is known that the number which are mobilized is under the control of follicle stimulating hormone secreted by the anterior pituitary, and the number can be increased by administering this hormone. The trigger that causes resumption of meiosis at the diplotene stage is luteinizing hormone, also secreted by the anterior pituitary gland. The trigger that causes resumption of meiosis at metaphase II stage is entry of the fertilizing sperm.

A simple solution to the technical problem of recovering mature unfertilized ova from human patients was suggested by Shettles (1953) based on the earlier work of Gregory Pincus and his colleagues. In 1935, Pincus and Enzmann showed in the rabbit that if oocytes in the diplotene stage were removed from the ovary and placed in culture, they would complete the maturation process. Soon after, Pincus and Saunders (1939) showed that human oocytes would also complete meiotic maturation in vitro. This pioneer work was later confirmed by Edwards (1965) with material collected at Johns Hopkins School of Medicine. Later, in collaboration with several investigators at Hopkins, attempts were made to fertilize 191 human oocytes matured in vitro after dissection from ovarian fragments (Edwards, Donahue, Baramki and Jones, 1966). They were unable to fertilize human eggs with certainty and concluded that the techniques at their disposal were too inefficient to be useful. A possible improvement in technique was reported 3 years later (Edwards, Bavister and Steptoe, 1969). In studies on capacitation and in vitro fertilization in hamsters, a modified Tyrode's solution was developed which



very significantly increased the fertilization rate (Bavister, 1969).

The use of this physiological saline was claimed to improve the fertilization rate of human oocytes recovered from ovarian tissue removed at surgery and matured in vitro. Several investigators were skeptical about the significance of this work (Rothschild, 1969; Mastroianni and Noriega, 1970; Brackett, Seitz and Mastroianni, 1971; Biggers, 1972), in that the criteria used to claim in vitro fertilization were inadequate, as in the earlier work in non-human species prior to Chang's use of genetic markers.

By this time, it was clear that another approach to the fertilization of human oocytes in vitro was required. In retrospect, the move to a new procedure was wise since it is now known that oocytes allowed to mature in vitro may not do so normally.

Chang (1955) had shown that many rabbit oocytes matured in vitro, then fertilized in vivo, would not form blastocysts and none developed to term. Cross and Brinster (1970), using mice, only obtained a very low yield of term fetuses. More recently, biochemical studies comparing the protein profiles of sheep oocytes matured in vivo and in vitro show significant differences (Warnes, Moor and Johnson, 1977).

The primary change in technique was to initiate the resumption of meiosis in vivo by the injection of luteinizing hormone [in practice human chorionic gonadotropin (hCG) is used]. The clue to this procedure resided in the paper by Chang (1955) who showed in rabbits that oocyte maturation could be induced in vivo by the injection of hCG. Oocytes matured in this way could be fertilized in vivo and produce normal young. Later, in the area of cytogenetics, Jagiello, Karnicki and Ryan (1968) induced resumption of meiosis in human patients with hCG and their data show that maturation proceeded at a rate

comparable with the normal process. Steptoe and Edwards (1970) refer to unpublished work on rabbits in which hCG stimulated oocytes were recovered shortly before the expected time of ovulation, allowed to mature in vitro and then fertilized in vivo. The manipulation resulted in normal term fetuses. Thus, the procedure was adopted of initiating resumption of meiosis by the injection of hCG to the patient and recovering the oocyte 32 hours later, 4 hours before the expected time of ovulation (Steptoe and Edwards, 1976).

Two secondary, but nevertheless important, changes in technique were also introduced as the result of developments in other areas.

One change concerned the method of oocyte recovery shortly before the expected time of ovulation. The customary approach was to gain access to the ovaries by laparotomy. Towards the end of the 1960s the technique of laparoscopy was adopted more and more for the diagnosis of gynecological disorders and for certain types of surgery on the genital tract. Steptoe was a pioneer in the application of this technique, and by the end of 1968, he had used it on 40 percent of gynecological admissions in his Department (1323 cases) (Steptoe, 1969). The technique proved ideal for the recovery of oocytes by the aspiration of Graafian follicles shortly before the expected time of ovulation (Steptoe and Edwards, 1970). Since then, the technique of laparoscopy has been adopted widely by gynecologists and is considered a safer and preferable procedure to laparotomy. Modifications of the technique for the recovery of oocytes have been described by Lopata et al. (1974) and Berger et al. (1975).

The other change in technique concerned increasing the yield of oocytes obtained from a patient. Normally only one oocyte is ovulated at each ovulation. In order to obtain more oocytes for in vitro fertilization, the technique of superovulation is used. This technique involves the injection of a gonado-

tropin with FSH activity during the early part of the menstrual cycle. The effect is to cause the growth of several Graafian follicles, each containing an oocyte which will respond to hCG. The technique was introduced for use in mice by Edwards and Gates (1959), and it is now widely used in many species including farm animals. Superovulation of women was first described by Jagiello, Karnicki and Ryan (1968) who administered human FSH to increase the yield of oocytes from patients with possible cytogenetic problems. With this technique, they obtained up to 14 ova per patient. Steptoe and Edwards (1970) introduced a similar technique using human menopausal gonadotropin (Pergonal) which also has high FSH activity. This technique was used in the case reported by Steptoe and Edwards (1976), which resulted in an ectopic pregnancy. Presumably it is also the technique used recently in the treatment of Mrs. Brown; details of the superovulation technique are not given in the recent letter to the Lancet (Steptoe and Edwards, 1978). Currently, the Australian group have used human pituitary gonadotropin (FSH) made available by the Australian Pituitary Advisory Committee (Talbot et al., 1976).

#### Fertilization and Embryo Culture

The culture techniques for the production of morulae and blastocysts from human ova fertilized in vitro have been described in several papers (Edwards, Steptoe and Purdy, 1970; Steptoe, Edwards and Purdy, 1971; Steptoe and Edwards, 1976). Their techniques have been gradually modified over the years. The procedure described in their last paper indicates that the oocytes recovered at laparoscopy are placed with spermatozoa in Bavister's medium for 18 hours. During this time, the sperm and ova complete maturation and fertilization occurs. The ova are then transferred to Ham's F10 culture medium supplemented with 15 percent of the patient's inactive serum. In this particular case,

a blastocyst formed in 4.25 days. It seems the human preimplantation embryo does not have the specific nutritional requirements of the mouse (Biggers, 1971).

and Steptoe

The technique appears to be fairly repeatable. Edwards (1977) reported on results with 27 patients superovulated with human menopausal gonadotropin and hCG. Twenty patients yielded preovulatory oocytes and blastocysts were obtained from 19 of these patients. The mean number of blastocysts was 1.7 (range 1-5).

#### Transfer of the Embryo into the Uterus

The recent letter of Steptoe and Edwards (1978) to the Lancet gives no information on the procedures used to maximize the likelihood of a successful transfer. The only information available is that reported by the same authors in 1976 concerning a case that resulted in an ectopic pregnancy.

It is well known that Edwards and Steptoe have treated many cases by in vitro fertilization, embryo culture and embryo transfer without success. The exact number of cases has not been published. There are probably three reasons why the success rate has been so low. The first reason arises from the fact that only a proportion of embryos would naturally go to term. From the data in Table 2, the expectation is  $31/69 = 45$  percent. The second reason is that the culture conditions may slow down development. As a result, the physiological state of the uterus advances beyond that of the embryo. This occurrence is likely to predispose failure since there is a simple rule that the embryo will wait for the uterus but the uterus will not wait for the embryo. The third reason, favored by Edwards and Steptoe, is that the hormonal treatment used for superovulation and induction of meiosis may disturb the endocrine events needed for implantation. Steptoe and Edwards (1976) attempted to over-



come this possibility by hormonal treatment. However, in 1977, they were considering freezing the embryos so as to transfer them one or two cycles later when the effects of the hormones administered to superovulate the patient had worn off. The use of the freezing technique depended on major advances in the preservation of laboratory and domestic species discussed extensively in a recent Ciba Foundation Symposium. Until Edwards and Steptoe publish full details of their recent cases, and all their failures, it is impossible to analyze the contributions of the various factors or techniques which have been involved.

#### Detection of Pregnancy

Shortly after implantation the embryo secretes hCG which can be detected in samples of maternal blood. The detection of hCG is therefore the basis of pregnancy tests, and it has been used routinely in all cases where embryos have been transferred to the human uterus. Three cases are recorded where hCG levels rose after the transfer (DeKrtzezer et al., 1973; Steptoe and Edwards, 1976, 1978). Implantation was not proven in the first case. The second case resulted in an ectopic pregnancy in the oviduct, while the third case resulted in a successful pregnancy.

#### Monitoring the Fetus

During the recent successful case, the wellbeing of the fetus was checked at 16 weeks by amniocentesis which allowed an examination of the levels of  $\alpha$ -fetoprotein and the chromosome complement. Both were found to be normal. Later, the growth of the fetus was checked by ultrasonic scanning and radiography. Shortly before delivery, the maturation of the lungs was checked

by the determination of the lecithin:sphingomyelin ratio. All tests indicated that a normal baby had developed. Louise Brown was then delivered by caesarian section.

#### EVALUATION OF THE CHARACTERISTICS OF THE EMBRYOS PRODUCED *IN VITRO*

There are two classes of question that may be asked in evaluating the characteristics of the embryos produced by fertilizing human ova in vitro. The first class concerns the properties of individual embryos, such as do the experimental conditions allow normal fertilization to occur in vitro? The second class concerns the properties of groups of embryos produced in vitro, such as how heterogeneous are they cytogenetically, and do the experimental procedures used in their production increase their heterogeneity?

#### Proof of *In Vitro* Fertilization

The problems of providing unequivocal evidence that proves the occurrence of fertilization has been referred to previously. The problems arise because fertilization is a multifaceted process. It involves two fundamental phenomena: firstly, the transmission of genetic information from the male by the incorporation into the ovum of the DNA carried in the sperm nucleus, and secondly, the activation of the ovum to complete meiosis and proceed with development. Both are accomplished by the entry of the fertilizing sperm into the ovum. The most direct evidence that fertilization has occurred is by the visual demonstration of a sperm within the ovum. This criterion has been achieved by Soupart and Strong (1974) using electron microscopy. These investigators matured 16 human ova in vitro and exposed them to spermatozoa. Fourteen were penetrated by one spermatozoa, one was penetrated by two spermatozoa and one was abnormal. The detection of two abnormal fertilizations out of 16 corresponds closely with the fertilization loss shown in Table 2. However,

the fourteen penetrated by one sperm cell only are not guaranteed normal development since the chromosomal constitution of either the sperm or ovum could have been abnormal through non-disjunction. Soon after the sperm enters the ovum, two nuclei form, one housing the female haploid set of chromosomes, and one housing the male set of haploid chromosomes. These nuclei are called the female and male pronuclei respectively. Their occurrence suggests only one sperm has entered the ovum, but provides no information that each carries a normal haploid set of chromosomes. Soon after their formation, the pronuclei fuse, a process called syngamy, the first cleavage division occurs, and the embryo passes through its preimplantation stages of development to the blastocyst stage. Nevertheless, all of these stages of development can occur even if the chromosomal complement is abnormal. This development can occur if the chromosome complement is normal but carrying an unmasked recessive point mutation. Alkaptonuria, the first genetic disease described by Garrod in 1900, is an example of a deleterious gene not affecting early development. It is also known that the development of a blastocyst does not depend on genetic information provided by the male at fertilization. Mammalian ova can be activated to develop parthogenetically (see Beatty, 1957; Graham, 1974, for reviews). Moreover, both haploid and diploid parthenogenomes can develop to the blastocyst stage (Kaufman and Sachs, 1975, 1976). The subsequent development of mouse parthogenomes in utero is very poor and no offspring have been produced. Recently, Surani, Barton and Kaufman (1977) have produced late term mouse fetuses containing cells descended from diploid parthogenomes by fusing such embryos and normal ones early in development to make a chimera. Thus, cells from diploid parthogenomes can probably function normally. The discussion of parthogenesis is always complicated by the results of Pincus (1939a,b), who claimed to have

produced five newborn rabbit diploid parthogenomes. The evidence was carefully reviewed by Beatty (1957) who concluded that in only three was the evidence satisfactory. Although Thibault and Ortevant (1969), and Chang (1954) failed to repeat Pincus' work, the extent of their experiments was inadequate to disprove an observation with an expectation rate of only 1:200. Thus, there is a very small possibility that a diploid parthengenome could be born. Such an individual would be female, as is Louise Brown.

Unequivocal proof of fertilization is the production of a male since such an individual can only develop if a Y chromosome is present. This chromosome must be provided by a Y-bearing sperm.

#### Heterogeneity of Embryos Produced by *In Vitro* Fertilization

It is obvious that the embryos produced by in vitro fertilization will show at least the variability that occurs as the result of natural mating. Thus, we may expect at least 69 percent of the embryos to be defective and unable to develop to term if reimplanted in their mothers. An additional, and more important aspect, is whether the techniques used for in vitro fertilization, culture and transfer increase the incidence of abnormality above that existing naturally.

An increase in the incidence of abnormalities could occur in four ways: induction of chromosome aberrations, increased rate of fertilization by abnormal spermatozoa, induction of point mutations and by physical and chemical teratogens. In 1973, Boué and Boué reported an increase in the level of trisomy among human abortuses from women who had been induced to ovulate. Since then, several reports have confirmed that an increase in



the incidence of chromosomal aberrations occurs as the result of superovulation in rabbits (Fujimoto, Pahlavan and Dukelow, 1974; Fujimoto, Passantino and Koenczoel, 1975), and in mice (Takagi and Sasaki, 1976; Maudlin and Fraser, 1977). The manner in which ova are exposed to spermatozoa in vitro may also result in an increase in triploidy (Frazer, Zanellotti, Paton and Drury, 1976; Fraser and Maudlin, 1978). If high concentrations of spermatozoa are used, the natural block to polyspermy may be overwhelmed resulting in polyspermic insemination. Edwards and Steptoe (1973) state that they examined the chromosomes of 15 human blastocysts produced in vitro and found no instance of triploidy. This observation is consistent with a normal incidence of 3 percent triploidy in all known conceptions (Jacobs et al., 1978). However, the sample is too small to reach a definitive conclusion. Edwards and Steptoe felt that their chromosome counts were too inaccurate to show the blastocysts were normal diploids; this is unfortunate, since they may have detected a high incidence of monosomies and trisomies.

There is evidence that some types of abnormal sperm are eliminated during the passage through the female genital tract. For example, it has been shown in women that few morphologically abnormal sperm reach the site of fertilization (Ahlgren, 1975). Similar observations have been made in mice, and it has been suggested that the utero-tubal junction is a barrier to abnormally shaped spermatozoa (Krzanowska, 1974). Spermatozoa carrying abnormal chromosome complements may not be prevented from reaching the site of fertilization, since diploid spermatozoa have been found in mouse embryos fertilized in vitro (Maudlin and Fraser, 1978). Studies of a different type have shown that after capacitation, spermatozoa recovered from the oviduct have a much greater fertilizing capacity than those recovered from the uterus (Cohen, 1974; Bedford, personal communication). Thus, fertilization of ova in vitro with

spermatozoa that have not passed through the female genital tract may be associated with an increased risk of fertilization with abnormal spermatozoa. The extent of this risk is unknown. The fact that in vitro fertilization requires much higher concentrations of sperm in the neighborhood of the ova compared with the concentrations found in vitro, may be partially explained by this phenomenon. The problem needs study since, as already shown, too high a concentration of sperm is likely to increase the incidence for polyploidy.

There is no experimental evidence relevant to the contribution of induction of point mutations and teratogenic effects from the techniques of in vitro fertilization and transfer of embryos. All of the methods do not involve the use of known mutagenic or teratogenic agents. Moreover, the preimplantation embryo is very insensitive to teratogens and x-rays compared to the sensitivity that develops at the time of organogenesis (Beck and Lloyd, 1965). Several studies have examined the effects of x-rays on preimplantation development in vitro. High acute doses may kill the embryos before blastocyst formation, or they may reduce the rate of cleavage. As a result, there are insufficient cells to form the inner cell mass, and a simple vesicle forms which is incapable of giving rise to an embryo (Alexandre, 1978). Other adverse agents may produce similar effects rather than cause anomalies affecting specific organs later in development.

If, in the future, freezing of human preimplantation stages is used to hold embryos for a more propitious time of transfer, the effects of low temperature may cause concern. This question has already been raised in the low temperature preservation of early embryos of genetically valuable mouse strains to avoid the expense of large breeding colonies. There is no evidence that freezing itself is mutagenic (Mazur, 1975). However, it has been suggested

that the cumulative effect of background radiation may increase the mutation rate since no DNA repair will occur at the temperature of liquid nitrogen. Recent studies by Whittingham, Lyon and Glenister (1977) have shown that 84 times background radiation of frozen mouse embryos for 27-29 months produced no detectable abnormal offspring.

## USES OF HUMAN EMBRYOS PRODUCED *IN VITRO*

### Treatment of Infertility

There is no doubt that infertility causes extreme stress to affected couples and the development of better methods of treatment is an important activity in medical research. The extent of infertility due to pathology of the oviducts in women in the USA is difficult to determine because most of the data available in specialized clinics and doctors' offices are non-random samples. Unfortunately, no well-designed epidemiological studies of human infertility have been made. However, a rough upper limit can be obtained as follows: There are 60 million women reproductively active in the USA; seven percent of couples are infertile, and a third of these are infertile because of sterility of the wife. Thus, there are 1,400,000 sterile women in the population. Pathology of the oviduct accounts for 40 percent of these cases so that there are about 560,000 women with diseased oviducts. Unfortunately, it is not clear what proportion of these women have normal ovaries that could be a source of oocytes. Pathology of the oviduct arises in several ways, such as endometriosis and salpingitis particularly due to gonorrhea. Since these conditions are increasing in incidence, the number of women with oviducal pathology is also increasing.

There are several surgical procedures available for the correction of

blocked oviducts. These are salpingolysis, resection and reanastomosis, fimbrioplasty and tubal implantation. The results obtained with these procedures are notoriously poor (Shane, Schiff and Wilson, 1976). Even if tubal patency is restored, the resulting pregnancy rate is far less (Table 4). Thus, a technique of establishing pregnancy which bypasses the oviduct would be a useful additional procedure.

Ovum transfer may also be useful when infertility is due to too few spermatozoa in the ejaculate (oligospermia). The sperm cells could be concentrated and used to fertilize ova in vitro which could then be transferred back to the uterus.

An important consideration is the likely efficiency of the technique developed by Edwards and Steptoe. The life-table shown in Table 2 indicates that, under normal conditions, the probability of obtaining a normal baby from a blastocyst is  $31/69 = 0.45$ . If it is assumed that the production of blastocysts and the transfer of embryos is fully efficient, the probability of obtaining normal babies after the transfer of one, two or three blastocysts can be calculated using the binomial distribution (Table 5). The number of oocytes that need to be collected from the ovary to give 1, 2 or 3 blastocysts can also be calculated. Since it is unrealistic to suppose the transfer technique is 100 percent efficient, similar calculations have been done assuming 25, 50 and 75 percent efficiencies (Table 6). From experience with embryo transfer in animals, it is more realistic to assume an efficiency of 50 percent. Thus, if one blastocyst is transferred, the chance of obtaining a normal baby is about 1 in 4. If three blastocysts are transferred, the chance of producing normal babies is raised to about 1 in 2, but this involves about a 1 in 100 chance of triplets.



Table 4

The rate of restoration of tubal patency and the resulting  
term pregnancy rate following surgery on the oviduct.

(from Shane, Schiff and Wilson, 1976)

<u>Operation</u>	<u>Tubal patency rate</u>	<u>Term pregnancy rate</u>
Salpingolysis	80-90	40-50
Resection and reanastomosis	80	25-40
Fimbrioplasty	20-40	10-25

Table 5

Probabilities of failure and the birth of singletons,  
twins and triplets following human blastocyst transfer  
[calculated from the life-table of Leridon (1973)] \*

<u>No. blastocysts</u> <u>transferred</u>	<u>Required No.</u> <u>Oocytes</u>	<u>Probability</u>			
		<u>Failure</u>	<u>Singleton</u>	<u>Twins</u>	<u>Triplets</u>
1	2	0.55	0.45	-	-
2	3	0.30	0.50	0.20	-
3	5	0.17	0.41	0.33	0.09

\* Assumes full efficiency of oocyte in vitro fertilization, embryo culture and transfer techniques.

Table 6

Probability of having a child (singleton, twin or triplet) following human blastocyst transfer, assuming different efficiencies of transfer.

<u>No. blastocysts</u> <u>transferred</u>	<u>Transfer Efficiency (%)</u>			
	<u>25</u>	<u>50</u>	<u>75</u>	<u>100</u>
1	0.11	0.23	0.34	0.45
2	0.21	0.40	0.56	0.70
3	0.30	0.53	0.71	0.83

Table 7

TRANSFERS OF OVA FERTILIZED *In Vitro*

SPECIES	STAGE OVA AT TRANSFER	NUMBER OVA TRANSFERRED	NO. RECIPIENTS(R) NO. R'S PREGNANT	NO. OVA IMPLANTED	NO. BORN	PERCENT ABNORMAL	REFERENCE
Rat	2-c	203	14/9	33 (in R) not given (in 4R)	(D.19)20 23	Not Avail. 50% <sup>1</sup>	Toyoda & Chang (1974)
Mouse	Morula & Blastocyst	299	Not given	Not given	111	-	Hoppe & Pitts (1973)
	2-c	30	3/1	10	9	-	Whittingham (1968)
	Blastocyst	32	Not given	Not given	5	-	Mukherjee (1972)
	Blastocyst	23	2/2	Not given	11	-	Mukherjee & Cohen (1970)
	2-c	80	8/2	Not given	(D.17)10 <sup>f</sup>	-	Miyamoto & Chang (1972)
	2-c	*95	19/3	Not given	(D.15) 3 <sup>f</sup>	-	Cross & Brinster (1970)
	2-c	*55	11/not given	Not given	13	-	Cross & Brinster (1970)
	Blastocyst	18	3/2	Not given	8	-	Parkening et al. (1976)
	2 & 4-c	16	2/2	6	4	-	Fraser & Dandekar (1973a)
	2 & 4-c	-f.c. 132	14/14	71	28	3.6% <sup>2</sup>	Fraser & Dandekar (1973b)

\* Immature oocytes were matured in vitro

• Ova were matured in vitro, in situ

Follic: Ova recovered from follicles

<sup>1</sup> Abnormality was microphthalmiax<sub>i</sub>: Recipients pregnant at implantation

f: fetus alive in utero

f.c. = Follicular cells

Surf: Ova recovered from ovarian surface

<sup>2</sup> Abnormality was splaylegx<sub>t</sub>: Recipients pregnant at term



TRANSFERS OF OVA FERTILIZED *In Vitro* (CONTINUED)

SPECIES	STAGE OVA AT TRANSFER	NUMBER OVA TRANSFERRED	NO. RECIPIENTS(R) NO. R'S PREGNANT	NO. OVA IMPLANTED	NO. BORN	PERCENT ABNORMAL	REFERENCE
Rabbit	2 & 4-c	+f.c. 125	14/9	16	9	11.0% <sup>2</sup>	Fraser and Dandekar (1973b)
	4-c	follic. 54	14/(11 <sub>i</sub> :5 <sub>t</sub> )	17	10	-	Mills et al. (1973)
	4-c	surf. 83	14/(9 <sub>i</sub> :5 <sub>t</sub> )	23	15	-	Mills et al. (1973)
	4-c	28	8/0	Not given	0	-	Brackett & Williams (1965)
	4-c	36	6/4	Not given	15	-	Chang (1959)
	4-c	6	2/2	4	1	-	Seitz et al. (1970)
	2, 4 & 8c	31	4/3	Not given	7 (3 died soon after birth)	-	Brackett et al. (1972)
	8-c	8	1/1	5	3	-	Brackett (1969)
	Not given	11	1/1	Not given	6	-	Bedford and Chang (1962)
	2 & 4-c	176	14/6	24	3	-	Brackett & Oliphant (1975)
	1-c	4	Not given	2	2	-	Seidel et al. (1976)
	2 & 4-c	37	Not given	9	5	-	
	8-c	67	Not given	6	4	-	
	Morula	38	Not given	16	15	-	
	Blastocyst	31	Not given	2	-	-	

It is important to recognize that the safety of the technique devised by Steptoe and Edwards relies on the natural elimination of abnormal embryos. Nevertheless, a proportion will not be eliminated, as occurs normally, and so an occasional abnormal baby will be born. It is therefore essential that the pregnancy be thoroughly monitored, using amniocentesis and any other available techniques. If abnormalities are detected, the patient and her husband, after counseling by her physician, will then have to decide whether to undergo an abortion. The problem with increasing the efficiency of the technique by transferring more than one blastocyst arises from the extra difficulties of monitoring the normality of more than one fetus, and then deciding what to do if abnormal and normal fetuses are developing together.

There is no information available which allows the prediction of the possible incidence of abnormal babies. Our only guide is the extensive work in in vitro fertilization, embryo culture and embryo transfer done in mice, rats and rabbits. A summary of these studies is given in Table 7. Only in two were abnormalities reported. Toyoda and Chang (1974) reported an incidence of 50 percent microphthalmia in rats, and Fraser and Dandekar (1973b) reported an incidence of 3.6 percent splayleg in rabbits. Why congenital aberrations occurred in only two out of 12 independent studies is unknown. A major concern is whether the different investigators were concerned and actively searched for congenital aberrations.

#### Fundamental Studies

In principle, any aspect of the process of fertilization and preimplantation development of the human could be studied using oocytes fertilized in vitro. Such work may lead to technological advances in the treatment of infertility or the control of excessive fertility. However, the heterogeneity

of the embryos should always be kept in mind. In the study of fertilization, for example, the fact that the sperm or ovum carries abnormal complements of chromosomes may not interfere with the results. Similarly, the study of the physiological processes in the preimplantation embryo may be independent of the chromosome content. In the words of E.V.Wilson (1893), "Embryogenesis begins in oogenesis", meaning that many events in preimplantation development have been programmed in the differentiation of the oocyte prior to ovulation and are independent of the new paternal set of genes. In work with multi-ovular laboratory species where many oocytes can be obtained, any biases that may arise from the heterogeneous population of embryos are minimized by randomization procedures. This precaution may be difficult to take with human embryos where only very small numbers are likely to be available. I suggest that work with human oocytes fertilized in vitro is only worth while if an important issue needs investigating, for example, if other non-human species show major differences in the phenomenon of interest. Furthermore, the work, involving human volunteers, should only be undertaken if efficiently designed experiments of adequate size are possible. Such requirements may need resources beyond those of individual investigators.

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SUPPLEMENT TO: IN VITRO FERTILIZATION EMBRYO TRANSFER  
IN HUMAN, JOHN D. BIGGERS, D.SC., PH.D.

Catherine Rice, Ph.D.

Table 1

The effect on embryonic viability of transfer to  
foster-mothers of *in vivo* fertilized ova of laboratory species



# M O U S E

STAGE OVA AT RECOVERY	STAGE OVA AT TRANSFER	SITE OF TRANSFER	# RECIPS. # PREG.	# OVA TRANSFERRED	STAGE PSEUDO- PREG. RECIPIENT (DAYS)	TREATMENT AFTER RECOVERY BEFORE TRANSFER	% OVA IMPLANTED	% BORN OR LIVE FETUSES	% ABNORM.	REFERENCE
day 2½	day 2½	uterus "	n.g./8 n.g./9	120 90	3½ 2½	- -	n.g. n.g.	0% 9%	0%	McLaren and Michie, 1956
day 3½	day 3½	uterus "	n.g./15 n.g./15	105 135	3½ 2½	- -	n.g. n.g.	10% 22%	0%	

# R A B B I T

STAGE OVA AT RECOVERY	STAGE OVA AT TRANSFER	SITE OF TRANSFER	# RECIPS. # PREG.	# OVA TRANSFERRED	STAGE PSEUDO- PREG. RECIPIENT (DAYS)	TREATMENT AFTER RECOVERY BEFORE TRANSFER	% OVA IMPLANTED	% BORN OR LIVE FETUSES	% ABNORM.	REFERENCE
1-cell	2-cell	oviduct	n.g.	25	syn.	c. 24 hrs	43%	12%	0%	Mills et al., 1973
2-cell	2-cell	oviduct	n.g.	35	syn.	-	32%	31%		
2-cell	4-cell	oviduct	6/5	53	-2	c. 24hrs.	38%	24%	0%	Fraser and Bandekar, 1973
2-cell (day 1)	2-cell	oviduct	6/0 5/0 10/3 8/7 24/21 10/4 8/0 13/0	86 60 129 97 239 116 104 156	-5 -2 -1 0 1 2 3 4,6,13	- - - - - - - -	n.g. n.g. n.g. n.g. n.g. n.g. n.g. n.g.	0% 0% 22% 38% 62% 19% 0% 0%	0%	Chang, 1950
4-cell (day 2)	4-cell	uterus	3/0 8/0 7/5 6/0 6/0	40 108 76 112 69 54	0 1 2 3 4 5	- - - - - -	n.g. n.g. n.g. n.g. n.g. n.g.	0% 0% 29% 28% 0% 0%	0%	
Early blast. (day 4)	Early blast.	uterus	5/0 6/0 8/3 7/5 17/13 9/5 7/0 9/0	66 74 107 78 167 90 81 109	0 1 2 3 4 5 6 7 & 10	- - - - - - - -	n.g. n.g. n.g. n.g. n.g. n.g. n.g. n.g.	0% 0% 25% 58% 58% 36% 0% 0%	0%	
Late blast. (day 4)	Late blast.	uterus	8/0 7/5 7/6 7/6 6/5	64 49 43 50 33	3 4 5 6 7	- - - - -	n.g. n.g. n.g. n.g. n.g.	0% 22% 46% 48% 36%		

RABBIT - continued

STAGE OVA AT RECOVERY	STAGE OVA AT TRANSFER	SITE OF TRANSFER	# RECIPS. # PREG.	# OVA TRANSFERRED	STAGE PSEUDO- PREG. RECIPIENT (DAYS)	TREATMENT AFTER RECOVERY BEFORE TRANSFER	% OVA IMPLANTED	% BORN OR LIVE FETUSES	% ABNORM.	REFERENCE
Late blast. (day 4)	Late blast.	uterus	7/4 6/0 3/0	42 50 11	8 9 10 & 11	- - -	n.g. n.g. n.g.	17% 0% 0%	0	Chang, 1950 (continued)
60 hrs.	60 hrs.	uterus	14/14	70	syn.	-	86%	77%	0%	Adams, 1960
60 hrs.	60 hrs.	uterus	14/12	60	syn.	-	87%	87%	0%	Adams, 1962

# R A I

STAGE OVA AT RECOVERY	STAGE OVA AT TRANSFER	SITE OF TRANSFER	# RECIPS # PREG.	# OVA TRANSFERRED	STAGE PSEUDO- PREG. RECIPIENT (DAYS)	TREATMENT AFTER RECOVERY BEFORE TRANSFER	% OVA IMPLANTED	% BORN OR LIVE FETUSES	% ABNORM.	REFERENCE
2,4-cell 2,4-cell 2,4-cell	2,4-cell 2,4-cell 2,4-cell	uterus " "	n.g. n.g. n.g.	18 16 20	syn. younger older	- - -	n.g. n.g. n.g.	60% 80% 10%	0%	Nicholas, 1933
day 2	day 2	uterus "	n.g. n.g.	n.g. n.g.	2 3	- -	n.g. n.g.	0% 8%	0%	Noyes and Dickmann, 1960
day 3	day 3	uterus " " "	n.g. n.g. n.g.	n.g. n.g. n.g.	2 3 4 5	- - - -	n.g. n.g. n.g. n.g.	0% 17% 0% 0%	0%	
day 4	day 4	uterus " " "	n.g. n.g. n.g.	n.g. n.g. n.g.	2 3 4 5	- - - -	n.g. n.g. n.g. n.g.	0% 26% 70% 5%	0%	
day 5	day 5	uterus " " "	n.g. n.g. n.g.	n.g. n.g. n.g.	3 4 5 6	- - - -	n.g. n.g. n.g. n.g.	0% 67% 58% 3%	0%	
day 1	day 1	oviduct " " " " "	n.g. n.g. n.g. n.g. n.g.	n.g. n.g. n.g. n.g. n.g.	-3 -2 -1 0 1 2 3	- - - - - - -	n.g. n.g. n.g. n.g. n.g. n.g. n.g.	0% 0% 12% 35% 50% 4% 0%	0%	Noyes and Dickmann, 1961
day 2	day 2	oviduct " " " "	n.g. n.g. n.g. n.g. n.g.	n.g. n.g. n.g. n.g. n.g.	-2 -1 0 1 2 3	- - - - - -	n.g. n.g. n.g. n.g. n.g. n.g.	0% 2% 12% 58% 0% 0%	0%	



RAT - continued

STAGE OVA AT RECOVERY	STAGE OVA AT TRANSFER	SITE OF TRANSFER	# RECIPS. # PREG.	# OVA TRANSFERRED	STAGE PSEUDO- PREG. RECIPIENT (DAYS)	TREATMENT AFTER RECOVERY BEFORE TRANSFER	% OVA IMPLANTED	% BORN OR LIVE FETUSES	% ABNORM.	REFERENCE
day 3	day 3	oviduct	n.g. n.g. n.g. n.g. n.g. n.g.	n.g. n.g. n.g. n.g. n.g. n.g.	-2 -1 0 1 2 3 4	- - - - - -	n.g. n.g. n.g. n.g. n.g. n.g.	3% 11% 3% 30% 48% 4% 0%	0%	Noyes and Dickman (continued)
day 4	day 4	oviduct	n.g. n.g. n.g. n.g. n.g.	n.g. n.g. n.g. n.g. n.g.	0 1 2 3 4 5	- - - - - -	n.g. n.g. n.g. n.g. n.g. n.g.	12% 33% 27% 20% 8% 0%	0%	
day 5	day 5	oviduct	n.g. n.g. n.g. n.g.	n.g. n.g. n.g. n.g.	0 1 2 3	- - - -	n.g. n.g. n.g. n.g.	0% 18% 37% 21%	0%	

Table 2

The effect on viability of freezing and  
thawing embryos of laboratory species

Research on the freezing and thawing of embryos of laboratory animals

The data presented in the attached tables should be viewed against the background of the research techniques used to obtain them. Researchers working in the field recognize that the ultimate test of viability for mammalian ova subjected to freezing and thawing is their ability to develop into normal offspring when introduced into the reproductive tracts of appropriately prepared foster-mothers. The use of foster-mothers, however, is expensive and time-consuming, particularly in species with protracted gestation periods. A variety of alternative techniques have been suggested (see Whittingham, 1978), but the two most frequently employed are to subject thawed embryos to morphological analysis, and to observe thawed embryos allowed to develop in culture. These two approaches produce similar conclusions as to the viability of frozen mouse embryos (Whittingham et al., 1977 a,b).

It has been found, however, that mouse embryos frozen at either the eight-cell or blastocyst stages, once thawed, evidence a delay in development. Thus, if frozen eight-cell mouse embryos are transferred directly after thawing into the uteri of pseudopregnant recipients, survival is significantly lower than after the transfer of untreated freshly collected eight-cell embryos or frozen/thawed eight-cell embryos cultured for 20 to 24 hours before transfer. The frozen/thawed eight-cell embryos cultured for 20 to 24 hours before transfer to foster-mothers, on the other hand, survive with approximately the same frequency as freshly collected eight-cell embryos transferred without treatment. The availability of a successful culture system for mouse embryos makes it possible not only to increase the survival rate of frozen/thawed mouse embryos,

but also to state that the freezing/thawing operation does not decrease significantly the likelihood of survival for transferred mouse embryos.

The work on rabbit embryo storage is less extensive than that of the mouse, but the viability of frozen/thawed embryos transferred to a foster-mother after thawing is less than that of freshly collected embryos transferred without treatment. An effort has been made to raise the survival rate of frozen/thawed rabbit embryos by maintaining the thawed embryos in culture for a period prior to transfer. The thawed rabbit embryos kept in culture, however, have not shown an increase in viability upon transfer to foster-mothers. This may indicate that culturing thawed rabbit embryos will not increase their capacity to develop into normal offspring, but the more likely explanation is that the culture systems available for rabbit embryos, unlike those for the mouse, are inadequate to support the resumption of normal development after freezing (Whittingham, 1977).

A major impediment to the storage of embryos of other species - rats, hamsters, guinea-pigs - is the lack of a culture system which can be used to sustain such embryos *ex utero*. This deprives researchers of one of the two preferred methods for evaluating the effects of freezing/thawing on embryos, and may account for the dearth of such research with some species.



# M O U S E

STAGE OVA STORED	TEMP. AT WHICH STORED	NUMBER STORED	% NORMAL EMBRYOS RECOVERED	DURATION OF STORAGE	TREATMENT ON THAWING	% NORMAL AFTER CULTURE	NUMBER TRANS- FERRED TO PREG. RECIPIENTS	NUMBER OF RECIPIENTS TOTAL	% FETUSES OR LIVE BORN	AB- NORM- AL	REFERENCE
Oocytes	-75°C	99	72%	5 min-3 hr	fertil. in vitro; c. to blast.	24%	11	3	27%	0	Parkening <i>et al.</i> , 1976
	Control				fertil. in vitro; c. to blast.	29%	12	2	66%		
Oocytes	-10°C	n.g.	n.g.	1/2 hr 3 1/2 hr	direct transfer	-	36 60	7 14	19% 12%	0	Sherman and Lin, 1958
Oocytes	-70°C -196°C	569 227	14% 12%	30'-25hr 30'-25h	fertil. in vitro	% fertil. 13 4					Tsunoda <i>et al.</i> , 1976
Oocytes	-196°C	223	55%	1-2 days	fertil. in vitro; c. to 2-cell	n.g.	83	10	16%	0	Whittingham, 1977
	control -196°C	n.g.	n.g.	1-2 days	c. to 2-cell c. to mor/ ear. blast.	n.g. 86%	35 33	3 3	34% 36%		
	control				c. to mor/ ear. blast.	80%	12	1	25%		
1-cell	-196°C			0.2-4h	direct transfer		36	5	22%		Whittingham <i>et al.</i> , 1972
2-cell	-78°C -196°C			0.2-4h 72 h	c. to blast. direct transfer	n.g.	25 118	8 13	20% 33%		
8-cell	-196°C -196°C	n.g.	n.g.	0.5-72h 12-78h	c. to blast. direct transfer	n.g.	80 76	21 10	38% 38%		
2-cell	-196°C -269°C			0.5-95h 0.2h+	c. to blast. direct transfer	n.g.	261 18	56 4	54% 61%		
8-cell	-269°C			0.2h++	c. to blast.	n.g.	7	1	43%		

\* Offspring produced normal offspring when mated together or with control mice

+ 141 hr at -196°C

++ 192 hr. at -196°C

# Fertilized in vitro and cultured to blastocyst stage

## M O U S E (continued)

STAGE OVA STORED	TEMP. AT WHICH STORED	NUMBER STORED	% NORMAL EMBRYOS RECOVERED	DURATION OF STORAGE	TREATMENT ON THAWING	% NORMAL AFTER CULTURE	NUMBER TRANS- FERRED TO PREG. RECIPS.	NUMBER OF RECIPIENTS TOTAL	FETUSES OR LIVE BORN	AB- NORM- AL	REFERENCE
4-8 cell											
HT	-196°C	321	44.6%	15-17 mths	c. to blast.	46%	118	12	11		Whittingham <i>et al.</i> , 1977a
PT		95	48.1%	15-17 mths		46%	40	4	4		
MU dp		320	42%	6-18 mths		40%	122	9	9	0	
XO		366	64%	9-18 mths		61%	187	21	18		
CBA,											
CBA-T6		180	55%	12-21 mths		44%	85	8	8		
8-cell	-196°C	n.g.	n.g.	up to 10.5 mths	c. to blast.	n.g.	306	43	39		Whittingham and Anderson, 1976
	-196°C	n.g.	n.g.	"	direct transfer	n.g.	80	14	12	0	
	control	n.g.	n.g.	-	c. to blast	98%	60	8	8		
	control	n.g.	n.g.	-	direct transfer	n.g.	107	9	9		
8-cell	-196°C	n.g.	n.g.	24h	c. to blast	50%	n.g.	n.g.	n.g.		Lyon <i>et al.</i> , 1977
				6-8 mths		53%	n.g.	n.g.	n.g.	0	
				10-12 mths		50%	n.g.	n.g.	n.g.		
	control			27-19 mths		47%	n.g.	n.g.	n.g.		
					c. to blast.	90%	n.g.	n.g.	n.g.		
8-cell	-79°C	112	96%	1-3 h	c. to blast	85%	7	3	1		Miyamoto and Ishibashi, 1977
	-196°C	129	96%		c. to blast	76%	7	3	1		
8-cell	-44°C	n.g.	n.g.	10 days	c. to blast	0%	0				Maurer and Bank, 1973
	-88°C	n.g.	n.g.	68 days		10%	0				
	-196°C	1126	93%	1 h		56%	n.g.	n.g.	n.g.		
				7 days		59%	n.g.	n.g.	n.g.		
8-cell	-196°C	360	52%	24h	c. to blast	49%	68	12	7		Whittingham <i>et al.</i> , 1977b
	control				c. to blast	96%	121	17	10		

## M O U S E (continued)

STAGE OVA STORED	TEMP. AT WHICH STORED	NUMBER STORED	% NORMAL EMBRYOS RECOVERED	DURATION OF STORAGE	TREATMENT ON THAWING	% NORMAL AFTER CULTURE	NUMBER TRANS- FERRED TO PREG. RECIPS	NUMBER OF RECIPIENTS TOTAL	% FETUSES OR LIVE BORN	AB- NORM- AL	REFERENCE
8-cell C5784/6J	-196°C	38	100%	189 days	c. to blast.	92%	35	6	42%	0	Whittingham and Whitten, 1974
BALB/CW <sub>2</sub>	-196°C	26	96%	222 days	c. to blast.	88%	22	6	50%		
		11	91%	189 days	c. to blast.	30%	3	1	27%		
		10	100%	222 days	c. to blast.	50%	5	1	40%		
8-cell	-196°C	n.g.	n.g.	12h-12 days	c. to blast.	65%					Wilmut, 1972
	control			-	c. to blast.	84%					
8-cell	-79°C	186	75%	30 min.	c. to blast.	69%	19	3	21%	0	Whittingham, 1971
Blast.	-79°C	50	68%	30 min.	c. 24hr.	01%	13	2	69%		
Blast.	-196°C	n.g.	n.g.	1 day 13 days 31 days	c. 17-20hrs.	n.g. n.g. n.g.	18 88 24	5 13 6	72% 59% 63%	0	Whittingham, 1974

# R A B B I T

STAGE OVA STORED	TEMP. AT WHICH STORED	NUMBER STORED	% NORMAL EMBRYOS RECOVERED	DURATION OF STORAGE	TREATMENT ON THAWING	% NORMAL AFTER CULTURE	NUMBER TRANSFERRED	NUMBER OF RECIPIENTS TOTAL PREG.	% FETUSES OR LIVE BORN	# AB- NORM AL	REFERENCE
2-cell 8,16- cell late morula 8,16- cell	-196°C	97	84%	1-21 days	c. 1-3h.	n.g.	38	5	4	37%	Tsunoda and Sugie, 1977
	196°C	69	74%	"	c. 1-3h.	n.g.	36	5	2	11%	
	-196°C	38	76%	"	c. 1-3h.	n.g.	14	2	2	64%	
	control					n.g.	27	4	4	63%	
8-cell	-196°C	n.g.	n.g.	2 days	dir.trans.	-	22	n.g.		18%	Whittingham and Adams, 1974
	-196°C	n.g.	n.g.	2 days	c. 48h.	74%	34	n.g.		0	
8-cell	-196°C	772	n.g.	1 day	c. 48h.	55%	140	36	20	29%	Maurer et al., 1977
	-196°C	355	n.g.	7 days	c. 48h.	57%	112	30	16	34%	
	control				c. 48h.	81%	84	18	12	38%	
8-cell morula	-196°C	n.g.	n.g.	1-6 mths.	dir.trans.	-	22	5	2	18%	Whittingham and Adams, 1976
	-196°C	n.g.	n.g.	1-6mths.	c. 48h.	n.g.	22	3	2	0	
	-196°C	n.g.	n.g.	1-6mths.	c. 48h.	n.g.	26	4	3	15%	
8-cell morula morula	-196°C	43	47%	n.g.	dir.trans.	-	10	2	1	10%	Bank and Maurer, 1974
	control	21		n.g.	dir.trans.	-	12	2	2	58%	
	-196°C	42	62%	n.g.	dir.trans.	-	46	6	3	15%	
	control			n.g.	dir.trans.	-	10	1	1	50%	
morula	-196°C	42	62%	n.g.	c.24h.	62%	28	5	3	7%	Maurer and Haseman, 1976
	control			n.g.	c.24h.	100%	30	3	3	10%	
morula	-196°C	n.g.	n.g.	at least 18 h.	dir.trans.	-	24	7	4	14%	
	control						24	7	4	43%	

<sup>a</sup> dyssymphysiis of the sternebra.



# R A T

STAGE OVA STORED	TEMP. AT WHICH STORED	NUMBER STORED	% NORMAL EMBRYOS RECOVERED	DURATION OF STORAGE	TREATMENT ON THAWING	% NORMAL AFTER CULTURE	NUMBER TRANSFERRED	NUMBER OF RECIPIENTS		% FETUSES OR LIVE BORN	# AB- NORM AL	REFERENCE
								TOTAL	PREG.			
8-cell	-196°C	198	47%	n.g.	dir. trans.	-	74	n.g.	n.g.	23%	0	Zeilmaker, 1977
2-cell	-196°C	144	73%	up to 3 mos.	dir. trans.	-	19	n.g.	n.g.	11%	0	Whittingham, 1975
4-cell	-196°C	67	55%	"	"	-	12	n.g.	n.g.	0	0	
8-cell	-196°C	128	48%	"	"	-	33	n.g.	n.g.	9%	0	



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HUMAN IN VITRO FERTILIZATION AND EMBRYO TRANSFER

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## 1. The beginning of life

Much of the public concern about human in vitro fertilization undoubtedly relates to the ethical issue of creating life outside the body. Therefore it seems important to ask at the outset what scientific evidence there is to support the view that fertilization represents the beginning of life?

Although there can be no doubt that the fertilization of an oocyte by a spermatozoon is normally an important event in the development of a new individual, we also know that fertilization is not an essential step in this process. Parthenogenesis, or the development of an egg cell into a new individual in the absence of fertilization by a spermatozoon, is the normal method of reproduction in a number of insects. In birds, parthenogenetically derived fertile male cockerels and turkeys are known to exist, and in mammals such as rats, mice, rabbits and guinea pigs, parthenogenones have been identified during the early stages of embryonic and fetal development, although they do not seem to survive until birth (Mittwoch, 1978).

Therefore the argument that fertilization represents the beginning of life cannot be supported on scientific grounds. It seems better to regard life as a continuum of gradually increasing probability of reaching adulthood. There may be a quantum increase in this probability at the time of fertilization in mammals, but there are still many hazards ahead of the fertilized egg if it is to implant and undergo normal embryonic development; even the unfertilized mammalian egg has some limited expectation of normal embryonic development.

## 2. Research aspects of human in vitro fertilization

In contrast to the obvious clinical applications of human in vitro fertilization and embryo transfer for treating infertility in women with bilateral occlusion of the fallopian tubes, there are significant applications of this technique for fundamental research in a number of areas. Indeed, it seems probable that these fundamental discoveries will far outweigh the rather restricted use of embryo transfer in their ultimate clinical significance. It would be

unfortunate if the Department of Health, Education and Welfare were to proscribe all research on human in vitro fertilization because of justifiable concern about the risks and benefits of the clinical procedure, only to halt the progress of much-needed fundamental research in this area. A number of specific examples of this basic research will illustrate the point.

a) Contraceptive Research. The mammalian oocyte is surrounded by a protein "shell", the zona pellucida. This contains specific binding sites for the spermatozoa of closely related species; unless the spermatozoa first bind to the zona, they will not be able to penetrate it and reach the vitelline membrane of the oocyte, where the fertilization process begins (Gwatkin, 1977).

If the proteins of the zona pellucida of hamsters are injected into mice, antibodies are formed which render the mice infertile (Gwatkin, Williams & Carlo, 1977), and passive transfer to mice of rabbit antibody raised against mouse eggs will make these mice temporarily infertile (Tsunoda, 1977). In vitro, it can be shown that the antibody works as predicted by preventing attachment of spermatozoa to the zona pellucida (Tsunoda, 1977). However, there may be an additional antifertility effect, since even if fertilization did occur, implantation would be prevented because the antibodies around the zona are known to prevent the blastocyst from "hatching" (Dudkiewicz, Noske & Shivers, 1975).

These studies in laboratory animals therefore show considerable promise as a novel form of immunological contraception. If research is to proceed in a logical manner towards the evaluation of this technique for human clinical use, the first step will be to see if antisera raised against the zonal proteins of a variety of animal species, including primates and the human, are able to block the fertilization of the human egg by human spermatozoa in vitro. If this effect can be demonstrated in man, the next step will be to characterise and if possible synthesise the zonal protein, so that enough antigen can be produced for human clinical trials. Antisera raised in humans would initially



### 3.

be screened for their antifertility action in an in vitro fertilization system, before proceeding to clinical trials in vivo.

If funds are not available for research into human in vitro fertilization, this promising line of investigation will come to a halt. The recent (October, 1978) World Health Organisation Advisory Group decision not to fund any research into in vitro fertilization where a human gamete or gametes are used underlines the need for continuing this type of basic research in North America.

There is another area of contraceptive research where human in vitro fertilization can provide an invaluable if not essential test system, and this relates to the development of male contraceptives. There is now abundant evidence to show that a variety of steroids - synthetic androgens, antiandrogens, or mixtures of androgens and gestagens - can be used to suppress sperm production by the human testis (de Kretser, 1976). But whilst it is a relatively easy matter to produce severe oligospermia, with sperm densities of less than 5 million/ml, it is extremely difficult to produce complete azoospermia. Provided that there are still some motile spermatozoa in the ejaculate, how will it ever be possible to reassure the man that he is indeed infertile? It would seem unethical to put the matter to the test by encouraging the man to have unprotected intercourse with his wife, who would then have to have recourse to abortion to make up for any failures of the male contraceptive. If it could be shown beforehand by in vitro tests that the few spermatozoa produced by men on steroid suppression therapy were incapable of fertilizing the human egg, this would provide sufficient reassurance to allow one to embark on a limited clinical trial. Without some such in vitro test of the fertilizing capacity of human spermatozoa, it is difficult to see how it will ever be possible to develop chemical approaches to male contraception, unless they result in complete azoospermia.

b) Infertility research. In contrast to the great advances that have been made in the diagnosis and treatment of infertility in women within the last decade, there has been little or no progress in our understanding of male

infertility. It is generally accepted that about 10% of married couples have an infertility problem, and although we cannot know for certain, it seems likely that the man is at fault in a significant proportion of such cases. The most useful index of male fertility is still the sperm count, but even this is an extremely imprecise guide. Nobody knows what a "normal" human spermatozoon looks like, and although a great deal of effort is devoted to scoring the proportion of morphologically "abnormal" spermatozoa in the ejaculate, we have no idea whether abnormal shape reflects abnormal function, apart from the fact that excessively large spermatozoa are diploid and hence incapable of normal fertilization (Seuanez, Carothers, Martin & Short, 1977). However, detailed studies of the chromosomes of early human abortuses show that in over 60% of cases there is a grossly abnormal karyotype which is presumably the cause of the abortion. These abnormalities are mainly due to errors of gametogenesis, and many are paternally derived (Short, 1978). Thus it must follow that there are many genetically defective spermatozoa in the ejaculate, although with present techniques we have no way of detecting them. It is also generally believed that if a man is oligospermic, with a sperm density of less than 20 million/ml, his fertility is greatly reduced. This is presumably not due to the low sperm count per se, since "bulking" a number of ejaculates in the deep-freeze and inseminating an increased number of spermatozoa at one time does not seem to improve the fertility of these men. The likely explanation is that whatever factor was responsible for the inhibition of spermatogenesis was also responsible for introducing some genetical, morphological or biochemical lesion into the few sperm that were produced, thus rendering them infertile. But hitherto we have had no way of knowing whether this was the case.

It would obviously be of great importance to assess the ability of spermatozoa from infertile men to fertilize eggs in vitro, but ethical and practical difficulties in obtaining adequate supplies of human eggs will necessarily restrict the scope of such investigations. Therefore one must welcome the recent exciting discovery by Rudak, Jacobs and Yanagimachi (1978), who have shown that it

is possible not only to get human spermatozoa to "fertilize" zona-free hamster oocytes in vitro, but that one can subsequently deduce the chromosome complement of the human spermatozoon from the karyotype of the fertilized egg. Thus for the first time we now have a technique that allows us to "crack open" the nucleus of the human spermatozoon and examine its genetic makeup. The consequences of this discovery are far-reaching, and cannot fail to throw new light on the intractable problem of human male infertility.

c) Cancer Research. One of the most fascinating tumours is the hydatidiform mole. It is a benign placental tumour, formed after fertilization of a "blighted ovum", following which the embryo itself fails to develop at all, whilst the placenta continues to grow as a cystic, grape-like structure which secretes, amongst other things, greatly increased quantities of human chorionic gonadotrophin. The mole usually reveals itself by haemorrhage, and if the uterus is not completely evacuated surgically, there is a risk that some of the molar tissue will go on to develop into one of the most malignant tumours, a chorioncarcinoma. The incidence of hydatidiform moles varies greatly in different areas of the world, being commonest in the Phillipines, although the reasons for these local differences in incidence rates are completely unknown. Recently, Kajii and Okama (1977) have made a discovery of the utmost significance in our understanding of the genesis of some human cancers. They investigated the chromosomal karyotype of a number of moles, and confirmed that they were invariably diploid, and XX. Using chromosomal banding techniques, they were able to deduce in a number of cases which of the individual chromosomes in the mole were derived from the father, and which from the mother. They made the amazing discovery that both sets of chromosomes in the mole are always derived from the father, with no maternal contribution to its genotype whatsoever. It therefore seems likely that the mole is caused by fertilization of an oocyte with a defective nucleus by a haploid, X-bearing spermatozoon. There is then a failure of the first cleavage division of the egg, so that the cell becomes diploid, and homozygous for all the paternal genes. Since a cell probably needs



at least one X chromosome to survive, no mole would result from a defective oocyte fertilized by a Y-bearing spermatozoon.

This exciting discovery opens up many promising lines of investigation. It should be possible in vitro to recreate the conditions necessary for the formation of a mole, and then to investigate the way in which this bizarre, benign placental tumour eventually become malignant. It might be possible to explain the geographical variations in incidence rates in terms of some environmental factor which influences the production of defective oocytes. And the fact that a defective human fertilization can give rise to such an unpleasant tumour should sound a note of caution to those who seek to exploit human in vitro fertilization and embryo transfer without adequate safeguards.

d) Basic research into man's evolutionary origins. Evolutionary biologists have always been fascinated by man's affinities to his four closest living relatives, the chimpanzee, pygmy chimpanzee, orangutan and gorilla, and it has recently been suggested that on anatomical and biochemical grounds the pygmy chimpanzee is most like the common ancestor from which man, the chimpanzee and the gorilla take their origin (Zihlman, Cronin, Cramer & Sarich, 1978). However, studies of the morphology of the spermatozoa in the four species, and spermatozoal DNA content, show that the spermatozoa of man and the gorilla are virtually indistinguishable from one another, whilst differing in a number of important respects from those of the orangutan and the two chimpanzee species (Seuanez, Carothers, Martin & Short, 1977). Since spermatozoal morphology has proved to be an excellent taxonomic guide in other more closely related species, there is a real possibility that man and the gorilla are far more closely related to one another than had hitherto been suggested. One way of investigating this proposition would be to carry out a series of in vitro experiments to assess the ability of spermatozoa from the four great apes to bind to the zona pellucida of the human egg, to penetrate the zona, and to effect fertilization.



Such an experiment, with its undertones of human-animal hybrids and genetic manipulation in a new sense of the word, would be abhorrent to many, and it is undoubtedly fear of public reaction that has prevented the experiment being performed to date. But the topic is mentioned here as it probably raises the greatest ethical dilemmas, and the scientific community at large would appreciate some ethical guidance. The obvious fear would be that if fertilization occurred in vitro, somebody would be tempted to implant the human/great ape hybrid embryo back into the uterus of an ape, or even a human, or more simply, to inseminate a female great ape with human semen. Some day, no doubt such experiments will be attempted, and it is impossible<sup>to</sup>/forecast their outcome. The ethical implications could be minimised if the experiment was strictly confined to an in vitro situation; a further safeguard would be to use immature human oocytes aspirated from preovulatory follicles, that are capable of being fertilized by human spermatozoa in vitro, but incapable of subsequent normal development. One could even irradiate the human oocyte prior to fertilization, thereby guaranteeing that no post-fertilization development would occur, or one could perform the experiment on dead human oocytes recovered from a cadaver at post-mortem, where fertilization would be impossible but the zonal sperm-binding mechanism should remain intact.

Whatever the ethical implications of such experiments, the results would be of the utmost significance in the assessment of man's phylogenetic origins.

### 3. Assessment of risks in human in vitro fertilization and embryo transfer

Having seen some of the spin-off from encouraging more basic research in the field of human in vitro fertilization, we must now consider the central issue of whether the practice of in vitro fertilization and embryo transfer, as pioneered by Edwards and Steptoe, is a safe procedure for routine clinical application.

In Great Britain and the United States it has been the practice to regard people and surgical procedures as innocent until proven guilty, but drugs as potentially hazardous until proved harmless. There would seem to be a case for considering in vitro fertilization and embryo transfer in the same category as

a new drug, which should be subjected to "toxicology testing" in animals and man, followed by limited human clinical trials, before being made available for general clinical use. How could these procedures be applied to human in vitro fertilization?

a) "Toxicology testing". Dr Biggers has reviewed for the Ethics Advisory Board all the laboratory animal experiments on the normality of offspring conceived following in vitro fertilization. It can be seen from the Table on page 40 of his document that there has been only a single experiment reported in the rat; in which half the 23 young born showed microphthalmia. In the mouse, 8 experiments have been carried out with 170 young born, all normal. In the rabbit, 17 experiments have been carried out, with 127 young born and only one or two minor abnormalities. There have been very few experiments in domestic animals (reviewed for the Board by Dr Foote) and no successful experiments in primates, aside from the birth of Louise Brown.

These results, although somewhat inadequate, are on the whole encouraging. The high abnormality rate in the rat experiment was probably not due to the in vitro procedure at all (Chang, personal communication) but nevertheless the experiment should be repeated. Whilst it would be helpful to have primate data, the constraints inherent in studying this problem in primates mean that it would be several years before adequate information would be forthcoming, and it would seem wrong to hold up progress until that information was available. The surgical procedure of embryo transfer seems to present few problems, and there is abundant animal evidence as to its safety and efficacy.

One area where more information is required is in the normality of human embryos produced by in vitro fertilization. Whilst fully admitting that it will never be possible to prove that they are completely normal, no matter what battery of tests are used, at least it should be possible to check for the existence of chromosomal abnormalities. It has often been argued by the proponents of in vitro fertilization that such an investigation would be irrelevant, since any embryo with gross chromosomal abnormalities would be aborted in the normal way, and other abnormalities such as Down's syndrome (Trisomy 21) could be detected by antenatal diagnosis, and the pregnancy terminated. However, such a study does seem both relevant and necessary on a number of grounds.

In the first place, if in vitro fertilization produced a high percentage of abnormal embryos, thereby significantly reducing the success rate of the procedure. this would surely suggest that the technique needed improving before being applied clinically. Better to discover its failings in the test tube than in the long-suffering infertile patient. Secondly, we know from the recent studies of hydatidiform moles, reviewed above, that abnormalities at the time of fertilization can lead to the production of a potentially malignant trophoblastic tumour that requires sophisticated chromosomal banding to detect. It would be important to establish that such fertilization errors did not take place in vitro. Thirdly, it is easy to say that genetically defective embryos, such as Trisomy 21, could be diagnosed and aborted, but one can hardly imagine how agonising such a decision might be for the infertile couple, who might see it as a decision between having a defective child, or no child at all. And finally, there is evidence in man and animals, some of it reviewed by Dr Biggers, that sperm selection occurs as the spermatozoa ascend the female reproductive tract in life, and one should beware lest an unselected population of ejaculated spermatozoa used to fertilize the egg in vitro result in an unacceptably high abnormality rate.

There may be some ethical difficulties involved in obtaining human oocytes from primed, preovulatory follicles in order to carry out these in vitro studies on the normality of the embryos, since the woman donating the oocytes would be required to give her consent for their use. One could aspirate the oocytes from the ovaries of women volunteers undergoing tubal ligation, although it would also be necessary to get their consent for the gonadotrophin treatment necessary to mature the oocyte in vivo. It would be most important to carry out such studies under the most strictly controlled conditions, in laboratories with access to the very best clinical, endocrine, and cytogenetical expertise. In this way it should be possible to determine the success rate of the in vitro fertilization procedure, and the normality of the resultant embryo, in relation to the endocrine state of the patient, and the stage of follicular and oocyte development at the time of follicular aspiration. The recent developments in ultrasonography which make it possible to visualise the developing Graafian follicle, and to detect



ovulation, might even make it possible to compare the success rate between follicular and tubal oocytes.

Such a planned, logical programme of investigation should not only provide reassurance about the risks, but should also help to maximise the chances of success of the procedure, and it is on the success rate that its clinical acceptance will ultimately depend.

One major difficulty will be the risk-benefit analysis of these human in vitro "toxicology testing" procedures. How can one judge what success rate is acceptable, or more importantly what percentage of chromosomal abnormalities is unacceptable? We have little enough information about the percentage of chromosomally abnormal embryos produced following normal fertilization, estimates varying from as high as 50% (Boué, Boué & Lazar, 1975) to as low as 10% (Jacobs, 1971). Furthermore, numerous studies point to the fact that the maximum probability of becoming pregnant in a menstrual cycle during which frequent intercourse takes place is only about 25% (Short, 1978), and it hardly seems likely that in vitro fertilization and embryo transfer will improve on this figure. It might be possible to obtain more precise information about the nature and extent of the chromosomal abnormalities following normal fertilization by examining eggs flushed from the uterine lumen of women. It has been demonstrated that fertilized eggs can be obtained by trans-cervical flushing 2-5 days after ovulation (Croxatto, 1974). However, this would be a major research project in its own right, and there are numerous ethical and medical difficulties in obtaining consent for the flushing procedure.

Perhaps the common-sense reaction should prevail. If it was shown that the chance of producing a chromosomally abnormal embryo as a result of in vitro fertilization was greater than, say, 50%, this would surely indicate that the technique needed improving before one could seriously consider embryo transfer to infertile patients. If the chance of any fertilization occurring at all in vitro was very low, this would again point to the need for technological improvements.

b) Clinical Trials. Assuming that it is possible to develop a reasonably successful in vitro fertilization procedure, that results in an acceptably



low incidence of chromosomal abnormality, the way would be open for carefully planned small-scale clinical trials of in vitro fertilization followed by embryo transfer. In addition to evaluating the success of the embryo transfer procedure itself, e.g. the relative merits of a transabdominal versus a transcervical approach, it should also be possible to determine the optimal stage of the embryo for successful transfer, and the optimal stage of the recipient endometrium. Bearing in mind the number of variables that are likely to influence the overall success of the procedure in terms of established pregnancies, it is obvious that much thought needs to be given to the planning of these clinical trials if one is to establish the most successful procedures in the least possible time.

#### 4. Conclusion

Whether or not human in vitro fertilization and embryo transfer becomes an accepted clinical procedure for the treatment of infertility will depend on its success rate. This can only be maximised by a carefully thought out programme of basic and clinical research.

Basic research in this area certainly deserves encouragement, since there is obviously much spin-off in terms of contraceptive development, treatment of infertility, a better understanding of cancer, and even new knowledge about man's evolutionary ancestry.

Clinical research must be aimed initially at establishing the safety of the in vitro fertilization procedure, and then at maximizing its success, and the success of the transfer technique. Funding in this area needs to be viewed in relation to the number of people likely to benefit from the procedure, and the degree of suffering it will alleviate.

Since the infertile couple will go to any lengths to achieve a pregnancy, no matter how low the success rate and how high the risks, it is probably the duty of the State to protect them from their overenthusiasm, and from unscrupulous commercial exploitation.



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SUMMARY OF THE PRESENTATION BY DR. P.C. STEPTOE AND  
DR. R.G. EDWARDS AT THE ROYAL COLLEGE  
OF OBSTETRICIANS

Roger V. Short, Sc.D., FRS



Dr Steptoe began the meeting by discussing patient selection and clinical management. They had confined their studies to couples wishing to have their own child where the wife had tubal defects. Most patients had been referred to them, following failed surgery for tubal repair as a result of pelvic inflammatory disease, ectopic pregnancy, pyosalpinx, or tubal ligation. All patients were under 36 years of age.

The criteria for selection were that the woman must have at least one normal ovary, a normal uterus, and a cornual blockage, and the husband must have normal semen.

The first procedure was to assess the normality of the woman's menstrual cycle, to analyse the husband's semen and culture it in order to exclude the possibility of viral or mycoplasma infection, to screen for toxoplasma and rubella antibodies in the woman, to perform routine cervical and vaginal bacteriology, and finally to carry out a laparoscopy for diagnostic purposes to see that the ovaries were free of adhesions. Laparoscopy could be difficult because of scars from previous operations. Only three patients were rejected because of extensive scarring, and all had had colostomies.

During the diagnostic laparoscopy, adhesiolysis would be carried out, accompanied by cornual diathermy, or ovarian suspension and salpingectomy.

In only 10% of patients had it proved impossible to recover an oocyte; in 2% of patients this was because the ovaries were too deeply buried. It was essential to free the ovary completely from all adhesions so that one could roll it around to get at all the follicles. Adhesiolysis was carried out by controlled thermocoagulation using teflon-coated scissors and forceps, and high-frequency diathermy was specifically avoided.

Oocytes were recovered following ovarian stimulation by gonadotrophins, or by clomiphene and chorionic gonadotrophin, or from normal follicles prior to spontaneous ovulation.

Possible future developments included embryo freezing, and use of donor sperm for fertilization.

The only contraindication was absence of ovarian function.

Indications for the operation were oviduct damage, oligospermia, prolonged idiopathic infertility, or the presence of sperm antibodies, or the control of sex-linked diseases.

R.V.S. Comment This seems rather an ambitious list of indications.

All the evidence from oligospermic men suggests that their fertility is depressed not just because sperm numbers are low, but because the few normal sperm that they do produce may in fact be abnormal in some way.

The relationship between sperm antibodies and infertility is far from clear and it seems doubtful if they are ever a significant cause of infertility.

The use of in vitro fertilization in prolonged idiopathic infertility is obviously a gamble.

For the control of sex-linked diseases, presumably they envisage the use of donor sperm and/or donor eggs.

As to the procedure itself, it is necessary to monitor the follicular phase and recognise the time of onset of the LH surge which precedes ovulation. Oocytes are recovered at laparoscopy under a short-acting general anaesthetic. It is most important to disturb the patient as little as possible, and hence local anaesthesia would be unacceptable.

A blunt 1.3 mm dia needle is used to aspirate the follicle. This is connected via a small trap to a 100 mm mercury vacuum pump: the trap can be filled by syringe with warm heparinised culture medium if desired. The gas used for inducing the pneumoperitoneum and for culturing the oocyte is 5% CO<sub>2</sub>, 5% O<sub>2</sub>, 90% N<sub>2</sub>.

The aspiration needle is introduced into the side of the ripe follicle via an outer cannula needle, which perforates an avascular area. A ripe follicle is approximately 3 cms dia. Analysis of steroids in follicular fluid helps to confirm whether or not it is a preovulatory follicle. Granulosa cells can also be obtained for studies in culture.



At this point, Dr Edwards took over.

Dr Edwards

The work started 10 years ago. The first problem to overcome was the stimulation of follicular growth and recovery of the oocyte just before ovulation. The routine procedure was to give injections of human menopausal gonadotrophin (HMG; Pergonal) on days 3, 5 and 8 of the menstrual cycle, followed by an injection of human chorionic gonadotrophin (HCG) on day 10-11, depending on the response (as measured by urinary oestrogen levels). The following table indicates the timing of ovulation in such patients following the HCG injection.

TABLE I

<u>Hours after HCG</u> <u>injection</u>	<u>No. of patients</u>	<u>No. ovulated</u>
29-31	59	1
31-35	59	2
35-37	5	1
37-38½	7	3
40-44	9*	6*

\* Data from Australian study

R.V.S. Comment The overlapping categories in column 1 are a curious error, repeated in other tables to follow. I may have made a mistake in column 2.

The eggs were recovered from the unruptured follicle and placed immediately in Tyrodes' solution, to which spermatozoa were added immediately afterwards. Fertilization occurred in 90-100% of cases. Spermatozoa were normally added within 2-3 minutes of the recovery of the egg from the follicle.

The problems of in vitro fertilization were solved 5 years ago and the techniques published. They have remained relatively unchanged since then.

For culture purposes, we have concentrated on Ham's F10 medium + the patient's own serum.

The fertilized egg grew well in culture in such a medium, and developed normally to the blastocyst stage. But the zona pellucida usually remained intact, and prevented the blastocyst from "hatching". However, sometimes hatching would occur spontaneously in culture, and the embryos would grow for 9 days, by which time they had expanded to 2-3 times the size of the zona. Equipped with this knowledge, it was decided to apply the technique clinically, attempting to reimplant embryos from the 8 cell to the blastocyst stage.

The problems now were when and how should one do the reimplantation, and when could one say that the embryo was growing normally or abnormally in culture? Growth curves were therefore established for 25 "normal" embryos in culture. (A graph was shown at this point). The extremes of the normal curve in culture were as follows:

TABLE 2

<u>Stage of embryo</u>	<u>Mean age at this stage of development</u>	<u>Age at which 95% of embryos were at this stage</u>
2 cell	35 hours	46 hours
Early blastocyst	112.7 hours	132 hours

If an embryo did not grow normally, as judged by this curve, it was not reimplanted.

For in vitro fertilization and embryo transfer, patients were accepted only up to the age of about 40 (Earlier, Steptoe had said they were all under 36).

Contrary to the experience in farm animals, it was decided to reimplant the embryos trans-cervically, not trans-abdominally. The following were the preliminary results:

TABLE 3

<u>Treatment for induction of ovulation</u>	<u>Treatment in luteal phase</u>	<u>No. of patients</u>	<u>No. of Conceptions</u>
HMG/HCG	0	13	0
HMG/HCG	Repeated injections of HCG	9	0
HMG/HCG	Repeated injections of HCG + Progesterone	5	0
HMG/HCG	Repeated injections of HCG + Primolut	16	2 ) 1 ectopic ) 1 HCG fell, ) followed by
HMG/HCG	Repeated injections of HCG, Progesterone and Primolut	10	1 ) abortion
HMG/HCG	Clomiphene	3	0
HMG/HCG	Bromocryptine	12	0
HMG/HCG + Clomiphene	0	2	0
Normal cycle + HCG	Repeated injections of HCG + Progesterone	7	0
		<hr/>	<hr/>
		77	3

These results were very disappointing, and it was concluded that the principal difficulty lay in abnormalities in the luteal phase following induction of follicular development with gonadotrophins. Studies were also carried out on the steroid concentrations in follicular fluid, measuring 8 different steroids. A computer was used to plot dendograms. In normal follicles, it could be shown that those which were destined to ovulate contained high concentrations of progesterone and oestradiol-17 $\beta$ , whereas non-ovulatory follicles contained low concentrations. Following stimulation with HMG and HCG, the follicular steroid patterns were bizarre. It seemed that the higher the oestrogen concentrations, the shorter the luteal phase, and many

patients had only 9 day luteal phases. So it was decided to abandon gonadotrophic stimulation of follicular development, and concentrate on normal follicles in the natural cycle.

R.V.S. Comment In view of the high success rate achieved by many investigators who have used exogenous gonadotrophins and/or Clomiphene to obtain pregnancies in anovulatory women, Edwards and Steptoes failures are unexpected. It would be surprising if abnormal follicular development or a deficient luteal phase were the true explanation for their lack of success. One wonders why two of the pregnancies which were detected by HCG levels failed to go to term. One hardly needs a computer to tell from the steroid pattern whether a follicle is likely to be ovulatory - the differences in steroid and gonadotrophin concentrations are quite obvious, as has been shown by the detailed studies by Dr K.P. McNatty, working in Edinburgh and latterly in Harvard.

If one is to exploit normal follicular development, it is essential to be able to predict the time of impending ovulation. The LH surge in urine offers an appropriate test system, provided that one can establish the time interval from the beginning of the LH surge to the time of ovulation. The time from the injection of HCG to ovulation was shown to be about 38 hours, and from the endogenous LH rise to ovulation about 21-36 hours.

There was a need to develop a simple laboratory test for urinary LH concentrations, and the best was found to be the Japanese Higonavis kit, which is a haemagglutination inhibition assay. It was shown to correlate quite well with a radioimmunoassay (RIA), and on occasions predicted the LH rise when the RIA failed to do so.

Work on detection of the LH surge commenced in November 1977, with the following results:



TABLE 4

<u>Description of LH surge</u>	<u>Number of patients</u>
No surge detected	6 )
Surge probably missed	2 )
Surge probably early	3 )
Surge successfully detected	68

11 failures

The next problem was to decide when to recover the oocyte in relation to the time of onset of the surge. There may be some circadian rhythmicity in the timing of the LH surge in women, since during the months of November-February it seemed to occur most commonly between 0600-1200 hrs.

Steroid concentrations were used to distinguish between ovulatory and non-ovulatory follicles, according to the following criteria.

TABLE 5

Mean steroid concentrations in follicular fluid, ng/ml

	<u>Oestradiol-17<math>\beta</math></u>	<u>Progesterone</u>	<u>Androstenedione</u>
Ovulatory follicles	1163	16208	28
Non-ovulatory follicles	29.7	30.2	213

42 patients were shown to have a single ovulatory follicle, and

3 patients had two ovulatory follicles.

The following table shows the time interval between the onset of the LH surge and laparotomy in relation to egg recovery:

TABLE 6

<u>Time from LH surge to laparoscopy</u>	<u>No. of follicles</u>	<u>No. with a follicular egg</u>	<u>No. with no egg recoverable</u>
15-18 hrs	9	7	2
18-21 hrs	12	9	3
21-24 hrs	14	12	2
24-27 hrs	19	14	5
27-30 hrs	5	2	3
30-35 hrs	6	1	5
	65	45	20

Of the 45 eggs recovered 44 were preovulatory oocytes. Following in vitro fertilization, 34 started to cleave, and 32 reached the 8 cell stage (this is somewhat less than the 90-100% fertilization rate claimed by Dr Edwards earlier in the talk).

It was reckoned that it took Dr Steptoe 80 seconds to expirate an egg from the follicle, and within a further 60 seconds, sperm had been added to it, and it had been placed in the incubator.

The next problem was that of the best stage of egg development for transfer. Three 8 cell transfers were carried out initially, and one resulted in a pregnancy. But after a total of 8 such transfers, no further pregnancies were produced. A third series of 7 or 8 transfers were then carried out, again without success.

On reviewing the evidence, it seemed that the first success resulted from a transfer carried out at midnight, and the second success resulted from a transfer at 10 p.m. Edwards then found published evidence for a diurnal rhythm in progesterone concentrations in animals, and thought this might explain his results in the human.

R.V.S. Comments From what one knows about time lags in mechanisms of hormone action, duration of receptor binding etc., this seems highly speculative.

It was therefore decided to embark on a 4th series of transfers, all carried out at night. This resulted in two pregnancies. In all the failures, there was no evidence (e.g. urinary HCG) of any pregnancy having even been initiated.

In summary, 32 reimplantations of fertilized eggs gave 4 pregnancies. The results are summarised in Table 7.

TABLE 7

<u>Time of transfer of fertilized egg to uterus</u>	<u>No. of transfers</u>	<u>No. of Pregnancies</u>	<u>Poor technique?</u>
Morning	7	0	3
Early afternoon	4	0	2
Late evening	21	4	7

Reviewing the previous HMG/HCG series, a similar trend for greater success at night is evident:

TABLE 8

<u>HMG/HCG stimulation</u> <u>Time of transfer</u> <u>of fertilized egg to uterus</u>	<u>No. of transfers</u>	<u>No. of pregnancies</u>	<u>Poor technique?</u>
Morning	8	0	1
Early afternoon	6	0	2
Late evening	12	3	2

The results were also analysed by the stage of the embryo at the time of transfer.

TABLE 9

<u>Stage of embryo at transfer</u>	<u>No. of transfers</u>	<u>Pregnant</u>	<u>Not Pregnant</u>	<u>Poor technique?</u>
6-8 cells	6	0	6	(2)
8 cell	17	2	14	2
16 cell	8	2	5	0
Morula	1	0	1	0
	—	—	—	—
	32	4	26	2

In the HMG/HCG series, one egg was at the 8 cell stage and two were blastocysts at the time of transfer.

Summarizing their results on oocyte recovery and in vitro fertilization followed by transfer in unstimulated donors:

TABLE 10

No. of patients admitted to study	79
No. of patients sent home	11
No. of patients undergoing laparoscopy	68
No. rejected because of adhesions	3
No. with no ovulatory egg recovered through errors of assessment of LH surge	9
No. in whom an egg could not be recovered from from follicle aspirate	11
Failure to fertilize egg <u>in vitro</u>	10
Failure of fertilized egg to cleave	3
Failure of transplanted egg to implant	28
Pregnancies	4

At this point, the story was again taken up by Dr Steptoe

Although they had tried surgical transfer of the fertilized egg, they concluded that the non-surgical approach was simplest and best. The technique was very similar to that used for artificial insemination. A 1.4 mm dia cannula was used. Steptoe stressed the need for a special theatre, used only for this type of operation, with strictest sterile precautions, and a laboratory immediately adjacent to the operating theatre. It was necessary to monitor pregnancies by ultrasound and amniocentesis for fetal karyotype and alpha-fetoprotein (AFP). In the 3 pregnancies that had been so monitored, AFP levels were normal.

In the case of Mrs Brown, she had developed pre-eclamptic toxæmia and there had been bouts of fetal tachycardia. Pregnancy had been monitored by human placental lactogen and oestriol. Amniocentesis had revealed a fetus with 46 XY karyotype. Since the L/S ratio in amniotic fluid was



elevated (Lecithin/Sphingomyelin) a Caesarean section was performed at 38½ weeks. The baby weighed 5 lbs 12oz, and no abnormalities were detected in over 40 tests. The baby now weighs 18 lbs 6 months after birth. The placenta was normal.

The second pregnancy was achieved in a woman with a history of infertility during 2 marriages. She was operated on for diseased tubes, and referred to Dr Steptoe, but then left the country. She returned to him several years later, in 1977. Following embryo transfer, she had a threatened abortion 7 weeks later, and finally aborted at 10 weeks. The embryo was karyotyped, and was found to be 69XXX. It was not possible to determine from banding studies whether the extra autosomal set was maternally or paternally derived.

R.V.S. Comment During in vitro fertilization, the oocyte is exposed to very large numbers of spermatozoa relative to those found in the fallopian tube in vivo. Thus there may well be an increased risk of dispermic fertilization leading to triploidy. This was not mentioned by Edwards or Steptoe.

The third pregnancy was achieved in a woman at the third attempt. On the first occasion, the operation was performed too late for oocyte recovery. On the second occasion, an oocyte was recovered, fertilized, and it cleaved, but no pregnancy occurred following transfer. On the third occasions, she became pregnant. On amniocentesis, the fetus was shown to be 46 XY with a large Y chromosome and an abnormal D chromosome. Both of these anomalies were also found to be present in the father. The mother aborted at 20½ weeks. The infant was born alive, but it died after 2 hours. It weighed 200 g, was 18 cms crown-rump length. No abnormality could be detected at autopsy in either the baby or its placenta.

The fourth pregnancy occurred in a woman at the second attempt. Amniocentesis showed a 46 XY karyotype. There was premature rupture of the membranes at 34 weeks, and the woman went into labour at 36 weeks and was delivered of a normal male infant weighing 5lbs 12oz whom she is breast feeding. He is doing well.

Dr Steptoe concluded his talk by saying that this new technique offered real hope for those suffering from pelvic inflammatory disease.

After prolonged applause from the 400 people in attendance at this private meeting, from which the press was excluded, Drs Edwards and Steptoe answered questions from the audience.

Q. What precautions do you take to avoid ectopic pregnancy? Do you put a clip on the tubes, or remove them? And what volume of fluid is used to transfer the embryo?

P.C.S. Cornual diathermy is used to occlude the tubes. The embryo is transferred in 0.07 ml of medium, and the pipette is checked afterwards to see that the embryo is not left behind. A single cannula is used, with the embryo in the distal 2 cms.

Q. Is fresh or frozen semen used?

R.G.E. Fresh semen, collected just before laparoscopy. We have not tried to clean up the semen, but this might be desirable if there are many dead sperm present. Published techniques are available.

Q. Does aspiration of the oocyte interfere with luteinisation of that follicle and subsequent function of the corpus luteum?

R.G.E. Aspiration does not impair luteinisation much. When normal follicles are aspirated, the luteal phase is always the normal 12-15 days.

Q. Would it be possible to remove the oocytes and freeze them, and then fertilize them later?

R.G.E. (Did not really answer the question). Some preliminary attempts have been made with Dr Whittingham to freeze embryos, but they have been unsuccessful so far, and the embryos are too precious to experiment with.

Q. Is it necessary to capacitate the sperm, and what concentration of sperm is used for in vitro fertilization?

R.G.E. The sperm are just incubated with the egg; the capacitation change occurs spontaneously. Sperm probably take 3 hours to become capacitated. The seminal plasma is removed by two washes, with mild centrifugation. The sperm are then resuspended in a good medium. The sperm should remain motile for 3 days in culture. One starts with  $10^6$  sperm/ml, but may dilute them down 3-4 fold for the in vitro fertilization.

Q. What stage is the egg at recovery, what medium is it in, and at what temperature is it cultured?

R.G.E. The methods are standard. Tyrodes or Earles solution is used, plus serum. After 18 hours, when pronuclear, it is transferred to Ham's F10 + 15% of the patient's own serum; it is gassed with 5% CO<sub>2</sub>, 5% O<sub>2</sub>, 90% N<sub>2</sub>. On recovery the eggs are in late anaphase or telophase with the first polar body.

Q. Why do you think transfer at night is less stressful?

R.G.E. I believe that there is animal evidence to support this concept of a diurnal rhythm. Prolactin levels are normal. I can't really explain why it seems best.

Q. Have eggs been put in earlier than at the 8 cell stage? Wouldn't the success of Estes' Operation (grafting ovary into uterine lumen) suggest this might be useful?

R.G.E. The reported successes of Estes' Operation, especially the earlier German reports, should be viewed with suspicion, according to a recent review by Dr C.E. Adams.

Q. How many attempts would you be prepared to make in one patient?

P.C.S. Keep on trying every 2 months until she become pregnant.

Q. On what day of the cycle does implantation normally take place?

R.G.E. All our results relate to the day of the LH surge, not the day of the cycle. 16 cell or morula probably best stage to transfer. Probably implants 6-7 days after LH surge.

Q. Is any re-buffering of the Ham's medium necessary? And if Vets can carry out these procedures in unhygienic surroundings, why can't the procedure be carried out in any ordinary hospital?

P.C.S. The Ham's medium is gassed with the 5% CO<sub>2</sub>, 5% O<sub>2</sub>, 90% N<sub>2</sub> mixture. The cultured embryo is reimplanted rapidly, using its own culture medium as vehicle. If any infection is present, fertilization will not occur. Infected semen is a problem.

Q. Do you only operate on primiparous women?

P.C.S. No, we accept multiparous women too.

Q. What guidance would you give for selection of patients?

P.C.S. We don't like them to be over 36.

Q. Are there any more pregnancies on the way that you have not told us about?



P.C.S. No. The work ceased in August 1978 and we have no facilities, but are hoping to have a hospital of our own where we can treat both private and National Health Service patients. Initially we would hope to treat about 10 per week.

This concluded the meeting. Drs Edwards and Steptoe left to a standing ovation.

R.V.S Comment It is interesting that there was no comment or questioning about risks, and absolutely no adverse criticism of the investigators. But if one looks critically at the results, the success rate is not high, and abnormal pregnancies have been produced. If both the gonadotrophin-induced and the normal cycles are combined, only 2 out of 7 detected pregnancies, based on a positive urinary gonadotrophin titre, resulted in term live births. In the talk, Edwards suggested that the triploid abortus might have been related to advanced maternal age, although there is no evidence that triploidy is related to either maternal or paternal age.

In retrospect, one wonders how it was possible to justify this procedure to women initially, without any assurance that it would work. Was it reasonable to carry out the surgical procedures involved in the absence of any knowledge about the normality of any embryos that might result from it? Has the woman who had the 20 week abortion benefitted from such an experience?

For the future there can be little doubt that many clinicians will attempt to carry out these procedures regardless of whether or not the U.S. and U.K. Governments make funds available for research in the field. Perhaps it will become another Christian Barnard situation. We must applaud the perseverance of the investigators and their technical achievement, even if we have misgivings about their ethical approach to their patients. In the wave of professional euphoria that follows, and spurred on by the potential financial

rewards in return for a relatively minor outlay in expenditure, many people will try to follow in Edwards and Steptoe's footsteps. But the relatively high failure rate may gradually cool both public and professional enthusiasm, and problems of litigation in the event of an abnormal pregnancy or an accident during amniocentesis, may provide a further disincentive. In the meantime, there is unquestionably a need for a careful, step-by-step scientific appraisal of the risks, benefits, and causes of failure of the whole procedure. It should be possible to design such studies without raising ethical objections. We need to know a great deal more about the normality or otherwise of embryos conceived in vitro before we can with impunity transfer them to the uteri of willing recipients who desperately want to have a normal baby.

*R. Steptoe*

Jan 29<sup>th</sup> 1979.

I have prepared this summary from notes that I made at the meeting, but there may be minor errors in it, especially in the Tables. However, I think I could vouch for the accuracy of Table 10, and also for all the major facts presented.

CORRESPONDENCE WITH PATRICK STEPTOE AND R.G. EDWARDS







DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
OFFICE OF THE SECRETARY  
WASHINGTON, D.C. 20201

ETHICS ADVISORY BOARD  
Westwood Building, Room 125  
5333 Westbard Avenue  
Bethesda, Maryland 20016

October 30, 1978

Dr. Robert G. Edwards  
Mr. Patrick C. Steptoe  
Oldham and District General Hospital  
Rochdale Road  
Oldham, Lancashire OL1 2JH  
England

Dear Dr. Edwards and Mr. Steptoe:

As you know, the world has watched with wonderment your remarkable accomplishment with in vitro fertilization. To many women like Mrs. Brown, your work brings great hope and excitement. To some, your work is a source of moral and ethical concern and a source of worry about possible forms and methods of reproduction in the future.

The Government of the United States is now faced with the question of whether to resume funding of human in vitro fertilization research. The first application for the support of such research, that of Dr. Soupart of Vanderbilt University relating to research on the fertilized embryo prior to implantation, has been approved scientifically and is now under review for ethical acceptability. Others are expected to follow, stimulated by your success.

The Honorable Joseph Califano, Secretary of the Department of Health, Education, and Welfare has directed the HEW Ethics Advisory Board to advise him concerning the ethical, legal and social issues surrounding human in vitro fertilization and embryo transfer. A roster of the Board and a copy of the Secretary's directive are enclosed.

In early September of this year, Dr. Charles R. McCarthy, Staff Director of the Ethics Advisory Board, spoke to Mr. Steptoe by telephone, first at Oldham Hospital and later in Fort Lauderdale, Florida. He informed Dr. McCarthy at that time that you intended to publish a detailed report of your research sometime around the end of 1978 after which you would both be willing to come to the United States and make a presentation to the Ethics Advisory Board.

The Ethics Advisory Board has completed a search and evaluation of all of the scientific and ethical literature published to date. However, the most important data, that which reflects your work of the last few years culminating in the birth of Louise Brown, has been unavailable to the Board. We are sure that you fully appreciate the significance of this data for the deliberations of the Board which must have as complete an understanding as possible of the scientific, social, legal and ethical issues involved in in vitro fertilization before making any recommendations to the Secretary.


We appreciate the intense demands that are being placed on you at this time. Nevertheless, we hope that you will agree to assist the Ethics Advisory Board by describing, either in writing or in oral presentation to the Board, more about your research, what it has established to date, and what may be expected in the future.

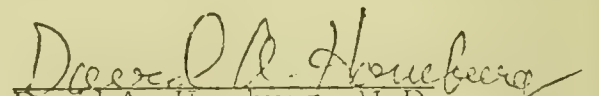
The next meeting of the Board will be held on November 10-11, 1978, in Seattle, Washington. After that, the Board will meet in Washington, D.C., on January 26-27 or February 2-3, 1979. We would be pleased if either or both of you could make a written or oral presentation to the Board on one of those days.

Of course, the Board will arrange to pay for your travel and expenses plus a reasonable fee for your services.

We know that you understand the importance to science of the Board's deliberations and the relevance of your work to those deliberations. We hope that you will agree to help.

Sincerely yours,

  
James C. Gaither, J.D.  
Chairman  
Ethics Advisory Board *by eff.*

  
David A. Hamburg, M.D.  
Vice Chairman  
Ethics Advisory Board *by eff.*

16th November, 1978.

Dr. James C. Gaither and Dr. David A. Hamburg,  
Ethics\Advisory Board,  
Department of Health, Education and Welfare,  
Westwood Building, Room 125,  
5333 Westbard Avenue,  
Bethesda, Maryland 20016,  
U.S.A.

Gentlemen,

Thank you for your letter of October 30th, 1978.

At the present time, Patrick Steptoe is travelling away from the United Kingdom and I cannot consult with him about the points raised in your letter of October 30, until he returns. We certainly wish to have as many patients as we can and also to help other doctors who wish to introduce this method.

We intend to give a scientific seminar at the Royal College of Obstetricians and Gynaecologists at the end of January. It is very difficult for me to travel away from the United Kingdom in view of my very heavy commitments here in Cambridge, although perhaps Mr. Steptoe is more free to move. Perhaps the best thing to do is for Mr. Steptoe and I to talk over your letter on his return and send you a joint answer then.

Yours sincerely,



R.G. Edwards



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

ETHICS ADVISORY BOARD

WESTWOOD BUILDING, ROOM 125,  
5333 WESTBARD AVENUE  
BETHESDA, MARYLAND 20016

December 5, 1978

Mr. Patrick Steptoe  
Oldham and District General Hospital  
Rochdale Road  
Oldham, Lancashire OL1 2JH

Dear Mr. Steptoe:

We are in receipt of Dr. Edwards' response to our letter of October 30, 1978 (attached) indicating that he would confer with you regarding the possibility of your presenting data relating to in vitro fertilization to the Ethics Advisory Board at its next meeting. We recognize the great demands being made on your time, but are confident that you understand how important it is to both scientists and infertile couples in this country that the Department of Health, Education, and Welfare make a sound and knowledgeable decision regarding possible support of research involving human in vitro fertilization. We hope that your plans to address the American Fertility Society at its meeting in San Francisco from February 3-7 will permit you to stop in Washington and meet with our Board on February 2nd or 3rd.


As you know, a major concern surrounding the application of in vitro fertilization and embryo implantation in humans is uncertainty regarding the safety and efficacy of the procedure. We believe you are in a position to dispel some of the uncertainty by providing data regarding such matters as: (1) the number laparoscopies necessary, on the average, to produce a fertilized ovum; (2) the number of attempts at implantation generally required before pregnancy is established; (3) the number of pregnancies established which have, and have not, gone successfully to term; (4) the proportion of embryos lost that appear to have some abnormality; and (5) the estimated length of time that a woman might expect would be required in order to achieve a successful outcome using your methods.

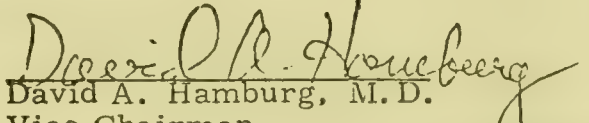
The Board hopes very much that you can make this type of information available at its February meeting, and also that you will be able to attend in order to answer any further questions that members of the Board might have. As might be expected, the Board is most hesitant to formulate final recommendations on this matter without the information that you can provide.



As might be expected, the Board is most hesitant to formulate final recommendations on this matter without the information that you can provide.

Cordially,

  
James C. Gaither, J.D.  
Chairman  
Ethics Advisory Board *by eff.*

  
David A. Hamburg, M.D.  
Vice Chairman  
Ethics Advisory Board *by eff.*

5th January, 1979.

Dr. James C. Gaither and Dr. David A. Hamburg,  
Ethics Advisory Board,  
Department of Health, Education and Welfare,  
Westwood Building, Room 125,  
5333 Westbard Avenue,  
Bethesda, Maryland 20016,  
U.S.A.

Gentlemen,

I am writing on behalf of Patrick Steptoe and myself in response to your letter of 30th October, 1978, and your recent telephone call.

We appreciate the situation now facing the Ethical Advisory Board and our professional colleagues in the United States over the funding of work on the clinical aspects of fertilization in vitro of human eggs, the growth of embryos, and their reimplantation into the mother. We feel strongly that any ethical decision about such work should be the responsibility of the patient, the doctor and the funding organisation. We are highly diffident about interfering with such a joint decision, especially in another country, by making a presentation to the Board.

We have formed our own opinions about the ethical, social and clinical aspects of the work and about the opportunities of future medical advances. We have no doubt about continuing our work to help the infertile. We equally intend to develop our methods for the reversal of sterilisation. Tubal occlusion could then be used by women to limit their fertility, relieving them of years of steroidal contraception, in the knowledge that they could conceive another child in the event of remarriage or the death of their family. We strongly believe that funds should be made available for this work in view of its considerable importance both to the patients concerned and for its wider implications in community health.

We desire to help the Board to make their decision in a different manner. We are fully prepared to send all copies of our papers as they are published, and to give advance notice of lectures dealing with our work. To go beyond this would place us in a position of publicly discussing ethical issues with other doctors and scientists in a foreign country with its own legal and social system. We do not wish to undertake this commitment, for we have dealt fully in the past with these complex issues at numerous symposia,

several in the U.S.A. Our participation in such meetings differs from that of other scientists and doctors, because for them the issues are abstract and impersonal. Our situation is very different, for we have taken our stand, defended it, and proceeded to bring it into clinical practice.

We trust that you will understand our position. Our impression is that the Board wishes to obtain the basic information from us on our recent work. We will be presenting our data at a meeting to be held at the Royal College of Obstetricians and Gynaecologists at 2.15p.m. on January 26th. Could we impress you to make every effort to attend, for the discussion will be free and open and you will have every opportunity to join in. We are now writing our papers, with the intention of publishing as soon as possible after the meeting.

Yours sincerely,

A handwritten signature in dark ink, appearing to read 'R.G. Edwards', written in a cursive style.

R.G. Edwards





IN VITRO FERTILIZATION AND EMBRYO TRANSFER

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In vitro fertilization of the human egg and the transfer of the product of in vitro fertilization to the uterus represent two separate and distinct issues. The latter has as its purpose, treatment of an infertile patient. The former is designed to explore the biological, biophysical and biochemical events in the human fertilization process. Techniques to achieve fertilization in vitro (within a glass) have been developed for egg and sperm of several laboratory animals. When these observations have been extended to the human subject, such studies, not unexpectedly, have raised important ethical questions. The purpose of this presentation is to review the techniques that have been developed for human in vitro fertilization, to evaluate the technical problems associated with these techniques, to consider the experimental and therapeutic purposes of such procedures and their ethical implications and to evaluate the appropriateness of embryo transfer at the present time.

#### Technical Procedures

##### Ovum recovery

Ovum recovery for in vitro laboratory observations may be carried out in volunteers during the course of a medically indicated abdominal operation (laparotomy) or laparoscopy. Laparoscopy, a technique for visualizing the abdominal contents, involves placing a telescope through a small incision in the umbilicus. It is used extensively in evaluating female infertility and for tubal sterilization.

The ovum is surrounded by specialized ovarian cells. The structure which contains the ovum is referred to as a follicle. During each menstrual cycle several follicles begin to "mature." The cells surrounding the ovum change, and the ovum itself becomes surrounded by clear follicular fluid. Ten to twelve follicles begin to ripen in this way but, in the absence of exogenous treatment, generally only one follicle (more in some cases of multiple pregnancy) continues to develop to full maturity. The remainder regress and become non-functional. Concomitantly the ovum, under the influence of pituitary hormones is being prepared for fertilization. This maturation process, occupies about 38 hours and results in a reduction in the number of chromosomes to half, the other half being cast from the ovum within a much smaller cell, the polar body. These changes are prerequisites for fertilization and therefore proper timing of ovum recovery is critical. The in vitro fertilization rate is reduced substantially if the ovum is extracted from its follicle too early during this maturation process.

During laparotomy or laparoscopy, ova are aspirated from ovarian follicles by needle puncture. They are then placed in a nourishing liquid culture medium. There is no evidence that removal of ova causes damage to the ovary. The normal female is endowed with four hundred thousand to five hundred thousand oocytes at birth, and thus there is no danger of depleting the supply of eggs.

In some centers patient volunteers are pre-treated with pituitary hormones (gonadotropins) in order to obtain suitably conditioned ova for fertilization. The use of pituitary hormones allows standardization of the menstrual cycle and simultaneous maturation of several ova containing follicles. These hormones have been used extensively for the induction of ovulation in infertile patients, and this treatment has been responsible for occasional production of



ovarian cysts and multiple births. Treatment with gonadotropins imposes a slight additional risk, that of the hormonal treatment itself, although thus far no complications have been reported when it has been used in association with ovum recovery experiments.

#### Ovum culture and insemination

On recovery, oocytes are cultured in vitro under controlled conditions. Semen is obtained by masturbation. Spermatozoa are separated from the semen by centrifugation, and washed; measured amounts are placed in culture chambers containing the oocytes. In several mammalian species, spermatozoa must be conditioned through exposure to the female reproductive tract before they acquire the ability to fertilize. This conditioning process, referred to as capacitation, does not appear to be as complicated or as prolonged in the human as in some of the lower mammals. It can be completed in vitro, possibly through exposure to the fluid recovered from the follicle (follicular fluid) or to special tissue culture solutions. Conditions of culture are critical if development is to proceed normally, and a proper balance of nutrients and carefully monitored temperature and oxygenation are important.

#### Transfer of the fertilized ovum.

If a cultured embryo is to be transferred to the uterine cavity for implantation, placement must be timed to coincide with development of the endometrium (uterine lining). At present there is no way to be sure that in vitro conditions are sufficiently well controlled for development not to occur faster or slower than would occur in vivo (in the living body). Normally the endometrium is progressively modified following ovulation. The endocrinologic events that occur following removal of an oocyte from its follicle (artificial ovulation) are still not completely understood. Discrepancy between the stage of development of the embryo and the level of maturation of the endometrium

could result in a high rate of implantation failure. Development of the endometrium to prepare it to receive the embryo may be accomplished with hormonal treatment. Steptoe and Edwards have used progestins, synthetic hormones, which have an action similar to that of progesterone. Progesterone is the hormone which is normally produced by the ovary after ovulation and which causes the endometrium to develop in preparation for implantation of an embryo. The use of certain progestins in pregnancy is associated with an increased risk of fetal abnormalities and is not recommended by the F.D.A. Progesterone itself has not, however, been implicated and could easily be used in place of its synthetic counterpart.

Experimental and therapeutic purpose of human in vitro fertilization

In vitro fertilization of the human ovum will allow insight into the human fertilization process. The potential clinical use of the technique with subsequent embryo transfer is a separate and more demanding issue. Since fertilization, on the one hand, and transfer of the product, on the other, involve risks of a different order of magnitude, the experimental and therapeutic purposes of each are best considered separately.

#### In vitro fertilization and culture

Since fertilization occurs in the fallopian tube (the conduit between the ovary and the uterus), the process is inaccessible and can be observed and evaluated best in vitro. Although animal models are useful in establishing important basic knowledge, one cannot confidently make inferences from the laboratory animal to Homo sapiens. Fertilization differs even among closely related laboratory species. Underestimating of human fertilization could result in development of systems for evaluation of human infertility or for more efficient methods of conception control. Examples of how in vitro fertilization could be used are considered below.

1. The effectiveness of antifertility agents could be tested in vitro. In this way medications could be initially evaluated without subjecting a patient to the effects of an untried drug.
2. The in vitro system could be used to evaluate the fertilizability of ova of patients with infertility and to assess the structural and biochemical normality of the conceptus in patients who have had repeated spontaneous abortion.
3. The effect of noxious agents, or teratogens, on the human conceptus (product of conception) could be evaluated in vitro. Such a screening system is much needed.
4. In vitro ovum culture and fertilization is useful for genetic studies in order to understand the mechanisms behind the production of such conditions as Down's syndrome (mongolism). Knowledge gained from such experimentation could lead to the development of methods to predict or prevent such unfortunate consequences of defective reproduction.
5. The recently fertilized ovum is a totipotential cell and in vitro culture systems could be used to advance our understanding of normal and abnormal cell growth and differentiation.

Laboratory procedures for human in vitro fertilization and ovum culture involve no significant risk to the donors of ova and spermatozoa. The pivotal issue relates to the status of the in vitro created embryo. Does the embryo constitute new human life, and if so is the experimenter responsible for its inevitable demise? The purposes for which the experiments are designed clearly involve cessation of culture with observations on the embryo from the one-cell stage through the blastocyst at six to seven days.

#### Embryo transfer

Following in vitro fertilization and culture, the ovum may be transferred to a recipient uterus for implantation. The obvious practical application of

this technology is to obviate the necessity of a functional fallopian tube. This approach may offer the only hope of having a child for patients with absent or severely damaged tubes.

Ovum donor treatment--removing an ovum from a female donor, fertilizing with a husband's spermatozoa, and returning it to his wife, whose eggs are defective (genetically abnormal or damaged by disease) or absent--has also been suggested. The male counterpart of this procedure is artificial insemination using a donor's specimen. In the latter the wife has normal ova and the husband has absent or defective spermatozoa. An extension of this approach is the transfer of the in vitro produced embryo to the uterus of a surrogate mother. This would allow an ovum donor with a diseased or absent uterus, or one who is unable or unwilling to proceed through pregnancy, to procreate without actually bearing a child.

For embryo transfer, in contrast to in vitro fertilization experiments without transfer, one is obliged to consider a complex risk-benefit ratio. The questions asked by the experimenter center about the risk to the mother (in the procedure itself), and the benefits to her (a successful pregnancy), as well as the risk to the fetus (possibility of deformity).

The risk of returning an in vitro fertilized embryo to the uterus must be scrutinized with great care. Although animal evidence that offspring are normal does not completely guarantee that the procedures would work equally well in the human, just as with other clinical treatments, extensive work in the laboratory animal should be a necessary requisite before proceeding with clinical trials. Statistically valid proof in animals that present techniques predictably produce normal offspring has not as yet been presented. Successful uterine transfer of in vitro fertilized ova has been accomplished in only two laboratory species.



Successful experiments have not been carried out in the monkey, whose ova are apparently more difficult to fertilize in vitro than are human ova. For this reason some of the commonly used laboratory monkeys, including the Rhesus monkey, may not be appropriate experimental models for this work. The Rhesus monkey has however, provided recent information that embryo transfer of in vivo fertilized embryos can be carried out at a relatively early stage in development, far sooner than would be predicted based on observations on the timing of normal transfer of eggs from the fallopian tube to the uterus. This suggests, then, that it may be practical to culture the embryo for a relatively short period of time in vitro fertilization, perhaps as short an interval as 36 hours, prior to transfer to the uterus. Culture systems become increasingly complicated with increasing embryonal age and if the embryo can, in fact, be transferred successfully at the four-cell stage, the possibility of damage would be reduced substantially. The availability of rapidly carried out determinations for LH (Luteonizing Hormone from the pituitary) levels now allows more accurate timing of ovum recovery in patients who are not treated with exogenous hormones, increasing the possibility of successful in vitro fertilization. Such new facets bring us closer to the time when it will be reasonable to offer this therapeutic modality to infertile patients. Prior to proceeding in the United States, in my opinion, additional extensive studies in laboratory animals should be encouraged so that we can have a statistically valid indication of the normality of fetuses produced following uterine transfer of in vitro fertilized eggs. Experiments designed to elucidate the events associated with human fertilization present yet another dimension, however, and these are to be encouraged. Evaluation of the genetic characteristics of invitro produced embryos would also provide useful information on which a decision as to whether or not to proceed with actual transfer could be based.



FERTILIZATION IN VITRO OF NONHUMAN PRIMATE OVA:  
PRESENT STATUS AND RATIONALE FOR FURTHER  
DEVELOPMENT OF THE TECHNIQUE

Kenneth G. Gould, Ph.D., MRCVS





## INTRODUCTION & BACKGROUND

The purpose of this report is to summarize and identify the present status of techniques applicable to in vitro fertilization of mammalian ova with a particular reference to nonhuman primates. Estimates will be made of the potential and need for development of nonhuman primate in vitro fertilization techniques.

Reports of the practicability of in vitro fertilization have appeared in the scientific literature since 1893 when Onanoff reported in vitro fertilization in the rabbit and guinea pig with fertilized ova cleaving to the 8-cell stage. Onanoff also claimed that fertilization followed intraperitoneal insemination, a technique more recently reinvestigated for use in the rabbit (Hadeck, 1958; Mroueh & Mastroianni, 1966) and primate (Van Pelt, 1970). As early as 1930 a reported technique for in vitro fertilization of rabbit ova was used to investigate the possibility of cross-species fertilization (Yamane, 1930; Krasovskaya, 1935), a concept which is being revived (e.g. Hanada & Chang, 1976; Yanagimachi et al., 1976), using denuded ova. There were other claims in the 1930s of in vitro fertilization of rabbit ova where the workers, as in all instances cited thus far prior to 1960, made no attempt to control the temperature of the gametes during manipulation, or to use "capacitated" sperm. Of claims for fertilization in vitro made prior to the independent discovery in 1951, by Austin and Chang, of capacitation, only one (Smith, 1951) seems possibly valid. Smith incubated ova with ejaculated sperm in the presence of tubular mucosa and serum at 37°C, conditions under which some sperm might be capacitated in vitro and fertilization ensue.

The description of capacitation provided an important step in the ongoing development of study of male and female gametes. Study of in vitro

fertilization requires a study of the individual steps involved in the process including sperm approach to the ovum, capacitation of spermatozoa, penetration of the ovum by the spermatozoa, formation of pronuclei, and syngamy. Recent development of techniques and knowledge concerning in vitro fertilization have paralleled studies of gamete physiology which have included investigation of oocyte metabolism (e.g. Biggers, 1971; Brinster, 1969, etc.), oviduct fluid composition in primate and nonprimate species (e.g. Sherman, 1971; Mastroianni et al., 1969; Edwards, 1973), parthenogenic activation (e.g. Abramczuk et al., 1977; Balakier, 1976; Graham, 1974) and aspects of sperm physiology including the metabolism of epididymal sperm, ejaculated sperm, and sperm within the female tract. Extensive studies into the phenomenon of capacitation and decapacitation have been conducted with reference to the morphological and biochemical changes involved (e.g. McRorie & Williams, 1974; Hanada & Chang, 1976; Niwa & Chang, 1976).

Normal fertilization includes a large number of physiological changes in both male and female gametes which have as yet been incompletely described. With regard to the female gamete, successful hormonal control of the estrus cycle resulting in ovulation is an obvious prerequisite. Metabolic changes in the oocyte prior to fertilization have been described and the chromosomal changes associated with nuclear maturation are well recognized and can be observed and induced in vitro. Less certain in this regard, however, is the possible requirement for a "cytoplasmic maturation" (Chang, 1955) of the ovum prior to fertilization. A requirement for such a maturation has been invoked as a reason underlying the relative lack of success in fertilization of immature oocytes matured in vitro prior to exposure to spermatozoa. This aspect is discussed

below with particular regard to fertilization of the primate ovum.

Spermatozoa, subsequent to ejaculation, must survive the relatively hostile environment provided by the female tract for the duration of their transit to the site of fertilization. It is during this period that capacitation, which is now recognized as a change preparing the sperm to undergo the acrosome reaction, occurs. The normal fertilization process thus involves capacitation, the acrosome reaction, penetration of the sperm through the investments of the ovum, entry into the vitellus, activation of the egg, pronucleus formation, and syngamy. Austin (1961) quoted the work of several workers to show that unfertilized ova can tolerate the adverse conditions involved in collection and manipulation in vitro prior to fertilization, and that fertilized ova have an increased tolerance in this respect.

Criteria for the documentation of successful in vitro fertilization have been discussed extensively (Bedford, 1971; Brackett, 1975). They include observation of sperm penetration into the ovum, and pronucleus formation, together with the presence of sperm remnants; syngamy with subsequent correctly timed cleavage of the ovum; and demonstration not only of nuclear material within each blastomere, but ideally of the diploid X-Y chromosome complement. The successful reimplantation of such fertilized and cleaved ova into a female with the subsequent development of viable offspring is the ultimate criterion. If we intend to push these criteria to the utmost, it is better for the offspring to be male than female because of the phenotypic demonstration of the X-Y chromosome complement! Thibault (1969) described the fertilization process in terms of six discrete stages; he considered that observation of formation of pronuclei or of the changing size and migration of the pronuclei constituted

unquestionable proof of fertilization. Observation of the sperm midpiece, and swelling of the sperm head may not be usable criteria because of difficulty of observation in some species. The presence of two polar bodies is inadequate evidence because the first polar body may degenerate or divide, which occurs frequently in hamster and mouse ova, or parthenogenic activation may lead to extrusion of a second polar body as is observed with some frequency in nonprimate species.

In the light of the recent successful reimplantation of an in vitro fertilized human ovum with the subsequent birth of viable offspring, it is almost redundant to state that progress has been made in the field of in vitro fertilization of primate ova, although realization of the Orwellian vision of in vitro fertilization of human ova with genetic and microenvironmental manipulation of the developing conceptus to permit accurate prediction of the offspring phenotype is still in the future. The recent success of Drs. Edwards and Steptoe culminates a chain of claims and retractions concerning fertilization of human ova in vitro, which began with the reports of Rock and Menkin (1944) and Menkin and Rock (1948). Those reports and later reports such as those of Shettles (1953, 1955) were inadequate and left doubt as to the possibility of fertilization occurring due to the methodology involved. Later work under strictly controlled conditions demonstrated that fertilization in vitro of human ova was indeed possible, and suggested that the process as regards sperm capacitation was similar to that in the hamster, with capacitation of human sperm occurring in vitro in the presence of oviducal follicular fluid (Edwards, 1966, 1969, 1970; Jacobson, 1969, 1970), although this interpretation differed from the report of Seitz et al. (1971) in which capacitation in vivo was implied to be a requirement for successful



fertilization in vitro of human oocytes. A role for protein and steroid hormones in the fertilization process was also implied by the results of Soupart and Morgenstern (1973) and Hayashi (1963) who reported on human ova, matured in vitro which were fertilized by ejaculated spermatozoa following incubation in media containing follicular fluid and various steroid hormones. The report by Jacobson (1970) is deserving of particular interest because the authors claim that they demonstrated a diploid chromosome complement with specific demonstration of the Y chromosome in these cleaved ova. This would therefore indicate successful in vitro fertilization.

The methods used by Steptoe and Edwards for in vitro fertilization of human ova include recovery of mature oocytes at laparoscopy. They reported recovery of one to three preovulatory oocytes when aspiration was performed 32 hours after the administration of 5,000 i.u. HCG prior to the anticipated time of the LH surge. The recovery rate for oocytes was between 50 and 70% (Steptoe et al., 1976). Preovulatory oocytes were in diakinesis, metaphase I or metaphase II, and were capable of being fertilized within a "few hours". It is now recognized that nonovulatory oocytes are surrounded by tightly-packed corona cells or no corona cells (in the case of atretic ova) in contradistinction to the loose cloud of cells surrounding preovulatory oocytes.

Human sperm obtained at masturbation were prepared for in vitro fertilization by dilution with suitable medium followed by gentle centrifugation and removal of the seminal plasma. Steptoe and Edwards used a modified Bavisters medium (Bavister, 1969) which is Tyrode's solution with albumin, pyruvate and penicillin added. Fertilization was accomplished in Bavisters medium which had a pH of 7.4 maintained by a

bicarbonate buffer.

A further report of human fertilization in vitro has been provided by Lopata et al (1978). These authors used clomiphene citrate to induce follicular development. HCG was administered when increased urinary estrogen levels were detected. Fifty percent of oocytes recovered were fertilized in vitro under conditions similar to those used by Steptoe and Edwards. Reference is made in this paper to the occurrence of "...abnormal fertilization..." which, by inference refers to polyspermic fertilization. No evidence was presented for any subsequent development of such abnormally fertilized ova.

In summary, proof of fertilization in vitro as a reproducible, and hence useful, technique has been demonstrated for the rabbit, hamster, mouse, cat, rat, and human. It is unfortunate that non-human promates in general have proved less amenable to the study of the fertilization process in vitro.

### Present Status of Fertilization in Nonhuman Primates

At this time presumptive evidence exists for in vitro fertilization having been achieved in three species of nonhuman primate; only for the squirrel monkey, however, is this evidence sufficiently persuasive to be used in the immediate design and development of an animal model. Evidence of fertilization has been observed in the squirrel monkey, rhesus monkey, and the olive baboon (S. sciureus, M. mulatta, P. cynocephalus). Rhesus monkey oocytes have been inseminated in vitro by a number of workers under a variety of experimental conditions. However, aside from occasions on which apparent pronuclei and two or four-cell ova have been observed, nothing in the way of consistent results has been achieved (Kraemer, 1978; Brackett, 1978a; Gould, 1978). Additional reservations are required with regard to fertilization in the rhesus monkey (Batta et al., 1978) as a result of the observation of persisting cortical granules, degeneration and absence of sperm remnants in otherwise apparently fertilized ova.

More optimistic is a recent report (Marston et al., 1977) of the term development of offspring from fertilized rhesus monkey ova subsequent to recovery of cleaved ova from one oviduct and replacement into the contralateral oviduct of the same female. This demonstrates the possibility, given adequate synchronization of donor and recipient, of

continued development of very early stage embryos in nonhuman primates subsequent to in vitro manipulation. It must be remembered that the embryos in this case were in vivo fertilized. The ova in this study were implanted in the oviduct using a fine nylon canula which was attached to a micrometer syringe filled with sterile liquid paraffin. Five term offspring (three female, one male, one stillborn male) resulted from reimplantation of one, two and six-cell embryos.

An interesting observation in this communication regards the still-born which was the result of the implantation of 2-cell embryo with a ruptured blastomere. Further research is required before the significance of this observation will be clear.

Although attractive as an initial experimental approach, tubal transfer of early cleavage stage embryos cannot be considered an adequate experimental method for development of techniques further applicable to humans, because the clinical indications for such work in the human, reviewed more completely below, will presumably be based on obliteration or absence of the fallopian tube. In addition it appears that the timing for tubal transfers may be more critical than that associated with uterine transfers. Kraemer (1978) has observed the apparent in vitro fertilization and subsequent cleavage to the six-cell stage of one of more than 100 ova recovered from Papio cynocephalus (Olive baboon). Detailed ultrastructural analysis of this ovum, and of others which showed apparent pronucleus formation but failed to cleave, has not been reported.

Exciting progress has, however, been reported by Kraemer et al. (1976) with regard to embryo transfer. A late morula stage embryo was successfully transferred to a non-mated female who had a cycle synchronized with the embryo donor as judged by measurement of sex skin coloration, with



subsequent normal gestation. The embryo was recovered in tissue culture medium 199 with Hanks salts and 0.35 grams of sodium bicarbonate per liter, and held for 20 minutes at 32°C prior to reimplantation. Reimplantation into the uterine fundus was by surgical means at laparotomy, as opposed to transcervical implantation via a catheter.

The feasibility of in vitro fertilization has been best established in the squirrel monkey (S. sciureus). Following the initial report of Gould et al. (1973) in which ejaculated sperm preincubated in medium 199 with follicular contents were used to inseminate mature follicular oocytes, advancements have been made toward the development of a predictable means for obtaining fertilization in vitro of ova matured in vivo and in vitro by Kuehl and Dukelow (1975) and Dukelow and Kuehl (1975). In initial experiments sperm in the perivitelline space, extrusion of the second polar body, pronucleus formation and cleavage of ova to the 2-cell stage at an appropriate time were presented as initial evidence for fertilization in vitro. However, ova which cleaved were not subject to transmission electron microscopy for ultrastructural examination because an insufficient number was available for immediate examination and it was hoped that further development through subsequent cleavage stages would occur in vitro. It was possible, however, to demonstrate a nucleus within each blastomere together with a diploid chromosome complement. Complete karyotyping was not undertaken. The conditions for successful in vitro fertilization of squirrel monkey oocytes thus far reported have been summarized by Brackett (1978b). In the work of Dukelow and of Gould an important control comprising incubation of ova in the absence of sperm, which was recommended by Brackett and Williams<sup>(1967)</sup>, was utilized. No cleavage was seen following 72 hours of culture in 36 oocytes, 10 of which

matured to the first polar body stage, nor was it observed in 15 oocytes cultured for 72 hours by Gould et al. It appears that although parthenogenetic activation and cleavage has been observed (Hayashi, 1963) in primate ova, it is relatively difficult to induce (Abramczuk et al., 1977).

It is evident that the work with nonhuman primates needs to be further expanded, particularly with regard to provision of an adequate number of fertilized ova or embryos for verification by ultrastructural and chromosome analysis of successful in vitro fertilization and of the normality of early embryonic development. Such an approach is required prior to satisfactory evaluation of the success rate of reimplantation of in vitro fertilized embryos in these species.

At this juncture it is pertinent to evaluate the reasons for the rather poor results using nonhuman primates.

1. Sperm recovery. Current techniques and knowledge show that recovery of spermatozoa is not the limiting factor for fertilization in vitro of nonhuman primate ova. Sperm can be readily recovered from nonhuman primates as a result of masturbation, use of an artificial vagina (Fussell et al., 1967), or electroejaculation using either penile (e.g. Mastroianni & Manson, 1963), or rectal probe electrostimulation (Gould et al., 1978). Sperm recovered from any of these sources are morphologically normal and the semen parameters are within normal ranges. However, recent work has shown that the artificial vagina may provide a semen sample with a better motility and increased sperm concentration (at least in the chimpanzee) than the other methods (Gould, 1978).

2. Oocyte recovery. At the present time, oocyte recovery is best performed by aspiration of follicles within the ovary at the time of laparoscopy. Earlier workers and those using the squirrel monkey initially

used laparotomy mainly due to lack of suitable equipment for the newer technique. The recovery of human oocytes has been reported by Edwards and Steptoe following hormonal priming of the ovum donor with gonadotropins, HMG (Pergonal) and HCG; after priming with clomiphene and HCG; or after injecting HCG alone in natural cycle a few hours before the anticipated LH surge. The time of the LH surge was predicted from urinary hormone assays with a urinary estrogen output of at least 100  $\mu$ g per day being associated with satisfactory oocyte recovery. Under ideal conditions oocytes were collected from between 50% and 75% of the aspirated follicles with a higher proportion being collected from larger follicles. Identification of preovulatory oocytes by virtue of the surrounding mass of mucus containing a loosely dispersed layer of corona cells has been described (Steptoe, 1977). It appears likely at this time that better results are obtained by timing the oocyte recovery procedure to permit recovery of mature oocytes in metaphase II. There is some disagreement in the literature regarding the fertilizability of in vitro matured oocytes; Dukelow and Kuehl (1975) report the use of in vitro matured oocytes for in vitro fertilization (without subsequent reimplantation); Suzuki and Mastroianni (1968), however, reported a disappointing rate of fertilization in vivo following maturation and culture of oocytes for varying periods of time in vitro. The use of oocytes recovered from multiple follicles induced to develop by hormonal treatment with subsequent treatment with prostaglandins to induce ovulation (Batta et al., 1978) may not be satisfactory following the demonstration of abnormalities in ova recovered subsequent to such treatment. The authors suggest that abnormalities possibly result from asynchrony of ovulation and oocyte maturation.

3. Culture conditions for gametes. We have sufficient evidence from both primate and nonprimate species (e.g. Brinster, 1965, 1971; Mastroianni & Novieger, 1970; Kennedy & Donahue, 1969; Dukelow & Kuehl, 1975; Brackett, 1978) to predict suitable culture conditions for nonhuman primate ova and sperm in vitro. With awareness of the deleterious effect of improper temperature control, osmolarity, and acidity of culture medium, it becomes a matter of persistence to identify the most suitable medium for various nonhuman primate species. It could be anticipated that such media would be similar to those utilized by Steptoe (1973) and Edwards (1973a, b) for human gametes. They used Bavisters medium (Bavister, 1969) which comprises Tyrode solution with added albumin, pyruvate and penicillin. The pH of their medium was maintained at 7.4, with a gas-phase of 5% CO<sub>2</sub>, 5% O<sub>2</sub> and 90% N; and an osmotic pressure of approximately 285 mOsmols was described as being ideal for fertilization. Subsequent development was best attained in Hams F-10 medium supplemented with either fetal calf serum or serum from the recipient (Steptoe, 1977; Edwards, 1973; Gould et al., 1973). Prior to the recent reports in the popular press of successful in vitro fertilization and reimplantation by Steptoe and Edwards, they had reported development of 70% of ova into embryos following in vitro fertilization in this medium (Steptoe & Edwards, 1976; Steptoe, 1977).

4. Sperm capacitation. It appears that human and nonhuman primate sperm undergo a capacitation and acrosome reaction which is similar to that observed in nonprimate species. Evidence for the requirement of capacitation has been obtained on both a temporal (Marston & Kelly, 1968) and biochemical (Dukelow & Chernoff, 1969) basis. Initial work on in vitro fertilization with human and nonhuman primates (e.g. Seitz et al.,



1971; Gould et al., 1973) provided for incubation of spermatozoa within the female tract, or contact with female tract fluids, respectively, for a time adequate for capacitation to occur. Other workers used "semi in vitro" culture methods (e.g. Soupart & Morgenstern, 1973; Hayashi, 1963; Jacobson et al., 1970). More recent work provides evidence that capacitation and associated changes can occur under a completely in vitro culture situation (Stephoe et al., 1976; Lopata et al., 1978). This is similar to the situation reported for nonprimate species including the hamster and rabbit in which incubation in completely artificial media or alteration of ionic composition of the culture medium have been shown to be effective in inducing the changes associated with capacitation. Indirect evidence for the involvement of natural products, however, is provided by the observations of Dukelow and Kuehl (1975) in which fertilization of squirrel monkey oocytes appeared to be enhanced by culture in small volumes which would result in an effective increase in the concentration of such natural products that were present in the culture medium associated with the cultured gametes.

The question thus remains as to why experimentation with in vitro fertilization in nonhuman primates has been less successful than that in the human. It is possible to hypothesize that there is a degree of abnormality in oocytes recovered from nonhuman primates, resulting from exposure to abnormal hormone conditions as a result of the increased chronic stress of colony and caged environments. This possibility is, however, unlikely in light of the relative success of in vivo breeding programs of essentially identical animals. A second hypothesis would state that there are as yet unidentified problems regarding the culture requirements for successful maintenance of nonhuman primate gametes in vitro and this

hypothesis is rendered tenable by the fact that there are undoubted physiological differences between the nonhuman primates and man with regard to composition of oviducal fluid, uterine fluid, and follicular fluid.

It is evident that as yet inadequate funding and research effort has been applied towards elucidation of the specific requirements for in vitro culture needed for successful fertilization and continued development of nonhuman primate embryos in vitro (Brackett, 1978b).

#### Problems of in vitro fertilization

##### Abnormality associated with in vitro fertilization

##### 1) Embryonic

Fetal abnormality could be predicted to occur during the in vitro fertilization process itself. During fertilization in vitro the normal biological processes which act to remove abnormal spermatozoa during the passage through the female tract are not present. There is, therefore, the risk that the ovum may be penetrated and fertilized by an abnormal spermatozoon, or by more than one spermatozoon simultaneously, resulting in a fertilized ovum with an abnormal genetic complement. It is also possible to hypothesize that as yet unknown factors act to control the normality of ovulated ova, and that an ovum recovered directly from a given follicle could be abnormal.

Edwards (1969) points out that embryonic development problems could follow the use of human oocytes matured and fertilized in vitro. Oocytes of the rabbit and other species matured in vitro and fertilized in vivo (as was attempted in the rhesus monkey by Suzuki and Mastroianni, 1968) demonstrated pronuclear stages which appeared normal, but from which the resulting embryos had subnuclei and fragmented blastomeres and virtually

all died during the early cleavage stages. In vivo maturation of the oocytes, however, followed by subsequent in vitro fertilization permitted the development of full-term rabbit fetuses upon reimplantation.

With regard to trauma during the culture period and the results of exposure to abnormal chemical influences at the time of in vitro culture with possible teratogenic effects, the available literature dictates the conclusion that the preimplantation embryo is extremely resistant to such insults to its integrity. Embryos of mice, rabbits, sheep, cows and other species have been separated into individual blastomeres and reaggregated; single cells in an embryo have been destroyed; pieces have been removed from blastocysts for chromosomal analysis and large parts of the embryonic disk destroyed, yet these manipulations have resulted in no increase in the number of malformed fetuses. Such resistance is also noted after application of chemical agents to embryos prior to reimplantation (Kalter, 1968; Tuchmann-Duplessis, 1969; Perry, 1971). Mouse embryos can develop into normal offspring subsequent to storage at temperatures down to  $-269^{\circ}\text{C}$  and damage induced in cleaving embryos may actually be repaired prior to organogenesis (Hooverman et al., 1968; Whittingham et al., 1972). Human embryos have also been shown to be resistant to malformation during these very early stages of development, and it appears that rather than abnormal development, the effects of such agents on preimplantation embryos are represented by death or lack of implantation.

The reason for this remarkable independence may lie in the relative totipotentiality of each cell in the very early embryo in which one cell can, at any time, replace the others in their entirety. A marked change in susceptibility to noxious influences occurs after implantation, during

the period of organogenesis; however, the presently used and proposed techniques of in vitro fertilization and reimplantation universally invoke reimplantation of embryos prior to the time of natural implantation in the uterus thus avoiding this potential problem.

With regard to the possibility of polyspermic fertilization, Edwards reported (1974) that in human ova the fertilizing spermatozoa penetrated the egg membranes approximately three hours after initiation of culture, pronuclei were formed some 12 hours after insemination and, "as judged by their microscopic appearance, none of the preovulatory oocytes has been triploid after fertilization, for all of them possessed two pronuclei, and no other abnormal form of fertilization has been observed" (Edwards et al., 1969; Bavister et al., 1969; Edwards et al., 1970). The literature also demonstrates that under circumstances in which the human embryo has been permitted to develop to the morula and blastocyst stage, the timing of preimplantation development in vitro has coincided closely with such facts as have been reported about in vivo development (Hamilton et al., 1962; Croxatto et al., 1972).

There is of course a possibility that in vitro fertilized ova (as occurs in a certain percentage of in vivo fertilized ova), will be triploid as a result of the presence of a diploid pronucleus resulting from failure of extrusion of the first polar body. However, such triploidy and trisomy arising from fertilization in vitro will not be a problem unique to growing embryos in culture, for many human fetuses are known to be trisomic. Estimates of trisomy by Carr and others based on fetuses obtained in the first or second trimester of pregnancies currently approach 5% of all conceptions. These estimates are likely to be low for many trisomic fetuses die in utero, sometimes prior to the time of implantation. There



is no evidence that a triploid primate fetus will develop beyond implantation.

## 2) Maternal

Although at first sight it appears legitimate to question the risks to the mother associated with the procedures involved in in vitro fertilization and reimplantation, upon consideration it is evident that the analysis of such risks has already been undertaken in some detail because the individual techniques involved are all presently used on human patients and the risks associated with them are considered acceptable. Examples of this include the hormone treatment used to stimulate ovulation; the collection of oocytes by means of a surgical procedure; supplementation of the mother with hormone prior to implantation of the fertilized ovum; and reimplantation techniques used.

Hormonal treatment is frequently used to stimulate ovulation, and provided it is accompanied with consistent and careful monitoring of the urinary estrogen output of the patient it does not have an adverse effect on either the mother or the offspring. Such hormonal stimulation has been in clinical use over a period of years in treatment of anovulation and infertility and we are now well aware of such risks that exist concerning ovarian hyperstimulation. We must recognize, however, that treatments of this nature will have to be modified for most of the patients requesting in vitro fertilization, because such patients may have normal menstrual cycles and the correct dosage of gonadotropins or clomiphene will need to be carefully calculated with continual monitoring of urinary estrogen output.

Laparoscopy appears to be the most acceptable and useful technique

for oocyte recovery and has been performed in many thousands of women for other indications with a very low incidence of complications. Such complications which do occur have been reviewed repeatedly in the medical literature.

The risk to the patient associated with the puncture and aspiration of the ovarian follicle must be considered minimal as visualization of the ovary through the laparoscope is quite adequate to avoid damage to large blood vessels with subsequent risks of hemorrhage; and aspiration of, and injection of drugs into, the chimpanzee follicle has not been associated with any alteration of the menstrual cycle (Gould & Graham, unpublished). In addition, it is valuable to remember that in the human this procedure is likely to be repeated only a few times, and it has already been demonstrated in nonhuman primates that it can be used many times with no detectable influence on menstrual cyclicity or physical normality. Similar criteria can be applied to the surgical technique involved in implantation of the fertilized embryo into the uterine cavity. It would appear that the risk of physical damage and injury to the embryo recipient would be less than that associated with, for instance, cervical dilatation and recovery of an endometrial biopsy by curetage.

The risk of ectopic pregnancy is more real, especially in circumstances where cleaved ova are reimplanted into the fallopian tube. Due to the apparent restriction of the phenomenon of ectopic pregnancy to the human and its much lower incidence in nonhuman primates, the occurrence of this abnormality will be difficult to assess. Ectopic pregnancy per se, however, can be readily diagnosed in the human and is already a recognized clinical entity which can be treated with existing medical knowledge. In this context it is important to remember that the most likely indication

for this procedure would be in circumstances where there was irreversible tubal occlusion, thus implying an absence of adequate tubal material or tissue for reanastomosis, and the site of reimplantation in such a case would be restricted to the uterine fundus, with a subsequent reduction in the possibility of ectopic pregnancy. The detection of abnormalities in the fetus during pregnancy would be a problem very similar to the one already existing subsequent to in vivo fertilization and the constraints and success of such methods would be completely interchangeable with the in vivo situation.

At this time it is impossible to predict the variation if any, in percentage of abnormal infants to be born subsequent to in vitro and in vivo fertilization. The incidence of physical abnormality in infants born subsequent to in vivo fertilization and "normal" pregnancy is in excess of 1.5%. For example, the incidence of spinal bifida in infants in the U.S.A. (one of many recognized abnormalities) is more than 3 per thousand. The incidence of fetal abnormality must be greater than this, for these figures relate only to term deliveries. The number of embryonic deaths is not known (DHEW, 1978). Such evidence as is available from nonprimate species shows that there is no detectable difference in number of abnormal young born subsequent to in vitro fertilization and reimplantation. It is unfortunate in this context that the human provides us with the best statistical base for evaluation of the percentage of abnormalities in offspring; on a considerably smaller base it appears that the natural incidence of fetal abnormality is lower in nonhuman primates than it is in the human (Wilson, 1971).

From a survey of 2,950 births, Wilson and Gavan (1967) reported an incidence of external malformations among 12 species of 0.44%. This

figure agrees with reports of 0.48% at the Sukhumi Primate Institute (Lapin & Yakovleva, 1963) and 0.53% at the Southwest Foundation for Education and Research (Hendrickx, 1966). Higher incidence (up to 1%) has been reported for one breeding colony of squirrel monkeys (Cooper, 1968). It does appear, however, that the incidence of specific malformations differs between man and nonhuman primate, and between primate species.

The existence of such variation must be taken into account when planning to use nonhuman primates in studies of embryo abnormality.



RATIONALE for research on in vitro fertilization in nonhuman primates

Despite the recent success of in vitro fertilization with subsequent reimplantation in the human, it is still important that adequate research in nonhuman primates be conducted before the extensive use of in vitro fertilization techniques in man is sanctioned. It is evident from the above statements of current rates of fetal abnormality that there is a potential for the development of abnormal infants subsequent to in vitro fertilization and reimplantation. It will, however, be necessary to obtain more direct evidence of the relative rate of abnormality subsequent to in vitro fertilization. Obtaining such evidence would be one major reason for pursuit of research in nonhuman primates to develop an in vitro fertilization model, for such a model could provide answers to some questions raised above concerning the potential influence of polyspermy, fertilization of aged ova, and the incidence of fertilization by abnormal spermatozoa, in an environment in which such experiments could be conducted with the deliberate intent of provoking such effects. If, for example, it could be shown that there is a significantly higher risk of abnormal development associated with fertilization in vitro of ova recovered from patients or from animals above a certain age, or fertilization of ova aged beyond a certain period of time in vivo or in vitro, then this would provide evident constraints on the procedure as applied to man.

The development of a nonhuman primate model at this time is also required with regard to the future directions that research and clinical experimentation utilizing human embryos may take. At the present time we are considering a situation in which ova are recovered from a woman with blocked fallopian tubes who is, however, otherwise physically normal.

An oocyte will be fertilized, presumably with her husband's sperm, and reimplanted into the ovum donor. It is evident, however, that logical development in the application of such techniques will potentially involve the procedure of ovum collection and its use for insemination with subsequent reimplantation to an infertile woman in a manner analogous to that of donation of sperm for A.I.D. It is also possible to envisage a situation when, during a period of sickness in the female, possibly necessitating the removal of the ovaries and/or fallopian tubes, oocytes would be recovered for subsequent storage at low temperature and later fertilized and reimplanted into the original donor or a surrogate mother. Such applications would involve more extensive manipulation of the gametes and such procedures should be evaluated closely in nonhuman primates prior to application to man.

In this connection it is germane to mention the need for extreme care in conduct of in vitro fertilization technique as a result of the current legal situation which provides for recovery by an infant, or by a parent in behalf of an infant, for damage or injury resulting from any action taken by a third party prior to the conception of the child (Tedeschi, 1967). Such a legal attitude behooves the researcher and clinician to evaluate as thoroughly as is possible any possible deleterious influence of culture medium, etc. utilized in the in vitro fertilization process upon the subsequent development of the conceptus.

A third reason for increasing the amount of effort directed towards development of in vitro fertilization models in the nonhuman primates lies in the potential use of such models for direct studies of teratogenesis and the resistance of early primate embryos to harmful influences. Such models would permit evaluation of various agents and their effect on

ovulation, fertilization and cleavage, e.g. the effect of copper on the early development of primate embryos. Such models could provide valuable information on the reasons underlying the apparently high incidence of fetal abnormality observed in man. Such an in vitro fertilization model would preferably be developed in a nonhuman primate closely similar to man in regard to reproductive physiology, such as the chimpanzee. Use of a chimpanzee model would reduce to a minimum the uncertainty regarding the applicability of results obtained to man. The chimpanzee has been shown to be physiologically extremely similar to the human, both in the nonpregnant menstrual cycle and during pregnancy. Such a species provides the added advantage that when an in vitro system is available, with the feasibility of embryo reimplantation demonstrated, the offspring will be susceptible to tests not possible with nonprimates. It is, for example, possible to test mental development and cognitive behavior in the chimpanzee in a meaningful manner and thus detect the existence of more subtle abnormalities which could have arisen as a result of in vitro fertilization.

It must be recognized, however, that availability of this species is at present limited, and maintenance and development of such a model would be expensive. For economic reasons, then, it is to be recommended that effort also be expended to further development of the most likely model of nonhuman primate in vitro fertilization currently available, the squirrel monkey. Development of an in vitro fertilization model in this species would permit evaluation of larger numbers of offspring in a relatively short time period. With a regard to other potential areas of application of in vitro fertilization techniques, it is evident that development of a nonhuman primate model becomes even more important.

Such areas including the creation of hybrids between humans and other animals and development of embryos past the implantation stage by means of maintenance in a surrogate mother or by means of development of an artificial uterus will dictate the use of nonhuman primates. This requirement reflects both moral and ethical considerations as well as the current legal attitude concerning manipulation and injury to the viable fetus should subsequent death or malformation occur prior to delivery. There is no doubt in this author's mind that the availability of such an in vitro fertilization model in a nonhuman primate would permit the collection of much basic data applicable to man which would be of value both in promoting the normal development of in vitro fertilized human embryos and in understanding causes for the high incidence of fetal abnormality observed in the in vivo situation, and potentially aid in correction of that situation.

#### CONCLUSION

In vitro fertilization of human ova with subsequent reimplantation and development of a normal term fetus has been achieved. At this time there is no adequate documentation for fertilization in vitro with subsequent reimplantation and normal fetal development for any nonhuman primate species.

With regard to application of in vitro culture and fertilization techniques to human material for the purpose of alleviation of specific forms of clinical infertility, it appears that there is no unacceptable risk to the mother associated with the techniques required for collection and manipulation of the gametes in vitro. Further, available evidence does not suggest that there will be an incidence of fetal abnormality in excess of that already recorded as a result of conception in vitro.



Development of nonhuman primate models for in vitro fertilization and early embryo development should be awarded a high priority 1) to further establish the fact that there is no increased incidence of abnormality subsequent to in vitro fertilization, 2) to provide basic biological data which would be of value in reducing the rate of fetal abnormality observed in man under in vivo conditions, 3) to provide models for teratogenesis studies, and 4) to provide the necessary background data prior to expansion of the work involving human gametes with regard to development of techniques for gamete storage.



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A NONHUMAN PRIMATE RESEARCH MODEL OF DEVELOPMENTAL  
RISK FOLLOWING IN VITRO FERTILIZATION  
AND EMBRYO TRANSFER

Gene P. Sackett, Ph.D.





This paper describes the pigtail monkey (Macaca nemestrina) as a potential research subject for assessing developmental risks of in vitro fertilization with subsequent embryo transfer. Among these risks are embryo, fetus, and infant mortality; embryo, fetus, and placental abnormalities; and birth and postnatal developmental defects. With regard to postnatal abnormalities, special emphasis will be placed on possibilities for detecting growth and behavioral deficits in surviving infants.

Papers already presented to the Ethics Advisory Committee have described principles of reproductive biology, ova fertilization and embryo transfer technology, and research on embryos produced by these procedures. These topics will not be treated here except where pertinent to proposed experiments. This paper is basically a research proposal including (i) an introduction to the research problem, (ii) a discussion of some important criteria for an adequate primate model, (iii) information available on reproductive outcomes and offspring development in pigtail monkeys at the Washington Regional Primate Research Center, and (iv) a research plan. The plan will include hypotheses; procedures to be used or developed for ova capture, fertilization, culture, and transfer; design of specific basic studies; estimates of personnel and budget required to conduct the studies; and a list of scientists willing to participate in this research as collaborators or consultants.

#### THE RESEARCH PROBLEM

A surviving human (Steptoe & Edwards, 1978) and baboon (Kraemer, Moore, & Kramen, 1976) offspring have been produced by in vitro fertilization with implantation back into the mother's uterus. These achievements open new possibilities for clinical treatment of infertility and genetic disorders in humans.

They also afford new possibilities for studying fundamental mechanisms of reproduction and development in humans and in nonhuman primates. This is especially true for the study of behavior. Questions concerning genetic versus environmental determinants form the nature-nuture controversies plaguing theorists and philosophers for hundreds of years. In vitro fertilization and culture will allow investigators control over events surrounding conception and the actual gene composition of newly conceived individuals (e.g., Markert & Petters, 1978). As a research tool, embryo transfer is a method for prenatal crossfostering in which fetuses can be developed in females other than the biological mother. Such prenatal crossfostering will allow investigators to separate prenatal determinants of development from genetic and other pre-conception factors.

Practical and valid clinical and scientific use of these procedures depends on answering one major question: Compared with natural conditions, does in vitro fertilization and embryo transfer increase rates of death and developmental defects. One minimal requirement for studying this complex question is the ability to capture ova, fertilize and culture them, and produce viable transferred fetuses in sufficient numbers for valid statistical comparisons. A related minimal requirement is the availability of normative data concerning mortality and development under natural conditions.

Professor James Kraemer (personal communication) estimates the chances of producing live primate offspring using current methods of ova capture, fertilization, culture, and embryo transfer to be less than 1 in 100. He bases this on three documented cases yielding confirmed fetuses in over 300 known attempts with human or nonhuman primate ova. On the other hand, these

procedures routinely yield up to 60% success in bovine species and nonprimate laboratory mammals (e.g., Foote, 1978). This success rate difference may be due to differences in reproductive mechanisms between primate and nonprimate mammals (e.g., Diczfalusy & Standley, 1971). Alternatively, primate success rates may be low because of inadequate methodology. Better ova capture techniques and cultures and the availability of many embryo recipients who are synchronized in reproductive cycle stage with donors may be required. Thus, development of more efficient and reliable techniques will need to be part of a research effort using nonhuman primate subjects.

Freezing ova or producing them in large numbers by hormonal superovulation yields increased risk for embryo abnormalities (e.g., Foote, 1978). However, such embryos do not apparently develop into live fetuses. In nonprimate mammals few, if any, abnormalities have been seen in live offspring produced by in vitro fertilization and embryo transfer. Although there may actually be no abnormalities, these negative findings could have occurred because studies have not systematically looked for abnormalities in newborns and infants using sensitive measures. This is especially true for behavior. Neither cattle, rabbit, rat or mice infants have been adequately assessed to date in any published study. Furthermore, differences in transfer success rates and reproductive and developmental mechanisms suggest that nonprimate data may not be valid information for concluding that there are no effects of these procedures in primates. In sum, there appears to be no definitive information concerning risk for offspring abnormalities in either humans or nonhuman primates.

POTENTIAL PRIMATE MODELS FOR EMBRYO TRANSFER RESEARCH

The utility of an animal model for solving human problems depends on knowledge about humans and degree of similarity between humans and the model species on dimensions of interest (e.g., Biggers, 1978). Additionally, several specific requirements seem essential for an adequate primate embryo transfer model. These

include knowledge about reproductive biology, availability of detailed developmental norms, and a sufficient number of female breeders to provide ova and receive embryos while in the proper state for implantation. Developmental and reproductive information is available for chimpanzees and a number of macaque, baboon, and squirrel monkey species. These species are maintained in domestic breeding colonies and appear to be the most likely model candidates.

Chimpanzees most closely resemble humans in anatomy, reproductive physiology, and intellectual behaviors (e.g., Bourne, 1977; Swindler & Wood, 1973; Premack, 1976), and therefore seem to be the best model. Unfortunately, these great apes develop almost as slowly as humans, are very expensive to keep in captivity, and are an endangered species available for research only in relatively small numbers. Thus, their utility for identifying a range of abnormalities in a reasonably short time is quite limited. Conversely, squirrel monkeys are rapidly developing, relatively small, new world primates that can be bred and maintained fairly inexpensively. They are suitable for anatomical and physiological studies, and their complex social organization and reasonable intellectual talents make them also appropriate for behavioral research (e.g., Rosenblum & Cooper, 1968).

Macaques and baboons are old world primates varying markedly in size and behavior. The most common forms in large breeding colonies are yellow and anubis baboons and rhesus, pigtail, and crab eating macaques. Each species has an estrous cycle of about 28 days, similar in period and hormonal changes to humans (Diczfalusy & Standley, 1971). Also like humans, females cycle throughout the year. Squirrel monkeys have a shorter 7-13 day estrous cycle, and many females are seasonal and do not ovulate during some months (Rosenblum & Cooper, 1968). In terms of estrous cycle length macaques and baboons seem to be a better model than squirrel monkeys. Having continuous cycles, baboons and



macaques are also more likely to produce ova and be available as embryo recipients without need for potentially harmful hormonal treatments.

An important practical consideration for an embryo transfer model concerns identification of estrous cycle stages to bracket the time of ovulation and to synchronize large numbers of donors and recipients. Actual menstrual bleeding is not often observed in baboons and macaques, especially when animals are housed in social groups. Pigtail monkeys and baboons are valuable here. They have a large perineal swelling (upper thighs and buttocks) that can be used to identify the day of ovulation in 60-70% of females (White, Blaine, & Blakley, 1973). This succession of nontumescence, tumescence, and detumescence is easily observed and charted even when animals are housed in groups. Cycling can thus be tracked in hundreds of potential ova donors and embryo recipients by external signs alone. In squirrel monkeys and the other macaques blood hormone levels and/or vaginal smears are needed to track estrous stages. This requires capturing the female, a generally stressful procedure potentially detrimental to hormone physiology and behavior (Sackett & Holm, 1978).

The gestation period for baboons is about 180 days. For macaques, gestation ranges between 165-170 days. Infancy in macaques spans the first post-natal year, with reproductive maturity at 3-4 years for females and 4-5 years for males. Baboons have a longer immaturity period and are not reproductively mature as soon. A great deal is known about reproductive biology in each species. Although the general details of reproduction are similar, there are species differences and each of these species differs from humans in at least some fundamental ways (e.g., Diczfalusy & Standley, 1971; Ruppenthal & Reese, 1979). For example, humans differ from macaques and baboons in distribution

of cholesterol lipoproteins important for hormone production during pregnancy (e.g., McMahan, Clarkson, Lofland, Rhyne, & Sackett, 1979), and in sex steroid binding protein changes during pregnancy (Schiller, Holm, & Sackett, 1978). Exactly which species best matches humans in reproductive biology is thus unclear. Therefore, the basic requirement described next may be the best criterion for choosing among potential primate models.

Detecting quantitative abnormalities using an existing primate colony will depend on availability of normative data on the animals in that colony. Even within each species large differences in vital statistics are found between colonies. For example, average birthweights between three large rhesus colonies vary by over 25% (Ruppenthal & Reese, 1979). Most primate colonies do have information about reproductive success of individual animals and about offspring growth. However, this data is often in clinical record file cabinets, not easily accessed for statistical summary. Some colonies do maintain computerized records, and can generate norms for large numbers of animals. To be accurate and valid, such norms must be studied by subject and environment factors like sex, age, maternal parity, weaning ages, type of caging, seasonality, and wild versus colonyborn origin. As shown by work of Hird, Henrickson, and Hendrickx (1975), vital statistic values vary tremendously by such factors. Most published colony data and data kept for clinical and reporting purposes are not broken down by pertinent variables. Much of these data do not approach even minimum standards for use as baseline values. When unavailable, as seems to be the case for most colonies, such norms will have to be generated as part of the embryo transfer research. For most vital statistics this would take a number of years and hundreds of animals for sufficient baseline data to detect abnormalities with statistical reliability.

The problem for behavior development norms is even more critical. Individual differences are the rule in primate development. Nutrition, social, and environmental factors can influence behavioral development in a profound fashion. Of course, the extremes of behavioral retardation-- like physical abnormality-- are detectable with only a few subjects. Gross anatomical abnormalities, lack of species-typical neurological and behavioral reflexes, complete failure to learn under test conditions, and atypical psychotic-like interactions by infants with their mothers or agemates are obvious and have been produced and measured by many primate behaviorists (e.g., Harlow & Harlow, 1965; Ruppenthal, Arling, Harlow, Sackett, & Suomi, 1976). However, detecting more subtle quantitative deviancies depends on availability of standardized test information on many individuals subjected to the same postnatal rearing conditions. It is likely that only a few existing primate colonies will be able to provide this aspect of an embryo transfer model.

In summary, three basic requirements for a primate model include (i) a large number of individuals available for study, (ii) the ability to continuously track estrous cycles of many females over long time periods, and (iii) norms on reproduction, growth, anatomy, and physiological and behavioral development for evaluating similarities to humans and to detect abnormalities in the products of embryo transfer. Next we turn to the pigtail macaque to illustrate one possible model for approaching these requirements.

#### THE PIGTAIL MACAQUE AS A MODEL FOR EMBRYO TRANSFER RESEARCH

The Regional Primate Research Center, University of Washington, houses 1,100 pigtail monkeys among 1,500 total primates. There are 400 females and 50 males active in breeding among the 650 breeding age pigtails. About 80% of these breeders live in harem groups containing one male and 6-12 females (Blakley,

1970). The remainder are in timed mating cages for producing offspring with precisely known gestational ages. The pigtail population on January 12, 1979 was 506 wildborn and 593 colonyborn monkeys. Table 1 shows the distribution of this population by years in the colony for wildborns and by age for colonyborns. Almost all wildborns are of breedable age, as are colonyborn females that have reached four years of age. Animals seven years or older are fully mature adults.

Table 1. Distribution of 1,099 pigtail monkeys forming the Primate Center population on January 12, 1979.

Time in Colony or Age (Years)	Wildborn		Colonyborn	
	Females	Males	Females	Males
0-1	155	5	90	66
2	65	22	48	54
3	46	23	49	19
4	9	1	21	10
5	33	4	34	8
6	24	3	27	9
7	31	1	31	7
over 8	82	2	67	53

In this population there are about 200 females who could be immediately available as ova donors or embryo recipients. Many of these animals have had estrous cycles tracked routinely for several years. An additional 50-60 animals that are fully mature have failed to become pregnant due to adhesions and blockage of the oviducts, aging, hormonal deficiencies, and unknown reasons. These females are also available as potential embryo transfer research subjects. A subgroup of this population, described in detail below, habitually produce aborted, stillborn, premature, low birth weight, and/or neonatally dead offspring. This set of 45 females and 5 males who produce poor pregnancy outcomes, and a comparable set of controls who almost never have bad pregnancy outcomes, are also available as research animals.



Reproduction and developmental research is conducted in two Center facilities. The main breeding colony is located at Medical Lake, Washington, near Spokane. Most mating and rearing of offspring in social groups occurs here (Blakley, Morton, & Smith, 1972). Most experimental studies on pregnant females and offspring reared without mothers in a nursery occur in Seattle at the Infant Primate Research Laboratory located on the Medical School and Health Sciences Center campus. This laboratory is jointly sponsored and funded by the Primate Center and the Child Development and Mental Retardation Center. Twentyseven investigators using primates as obstetrical, pediatric, or neuro-behavioral models are active in this laboratory. The facility provides 24-hour care of healthy and medically high risk newborns, conducts routine measurement of growth and behavior, has an 'obstetrical' unit that monitors pregnancies and obtains measures and specimens during labor and delivery, and can rear offspring either with or without their mothers. Pregnant females and newborns come to the laboratory from Spokane via commercial jets. A study of over 1,000 transported animals revealed no evidence of abnormalities produced by these flights.

#### COMPUTERIZED ANIMAL RECORDS

A major Primate Center resource is its 15-year computerized colony record system. These records are archival for live and dead animals. The computer routinely generates vital statistics for the colony as a whole, all live or dead animals, and single individuals. The data base contains over 500,000 entries on 5,418 total pigtail monkeys. Among other dimensions, the computer generates norms for (i) conception rates and pregnancy outcome probabilities, (ii) deaths and survivorship statistics, (iii) body weight gain, (iv) disease incidences and causes of death, and (v) hematology and other blood chemistry values. These measures can be studied for variation by age, sex, origin as a

wild or colony born animal, age at weaning, season, experimental history, type of housing, number of prior conceptions or births and other factors. A number of studies have already been done using these records (e.g., Sackett, Holm, Davis, & Fahrenbruch, 1974) or are in progress. Tables 2 and 3 give breeder and offspring sample sizes available in these records as of January 12, 1979.

Table 2. Sample sizes for studying conception rates and pregnancy outcomes of pigtail monkeys from computerized records as of January 12, 1979.

	<u>Breeders With 1 or More Known Conceptions</u>					
	Wildborn		Colonyborn		Total	
	Females	Males	Females	Males	Females	Males
Number of Animals	696	92	169	50	865	172
Mean Number of Conceptions	3.3	14.0	2.6	13.5	3.2	11.4
SD of Number of Conceptions	2.3	11.9	1.7	14.4	2.2	17.1
Total Number of Conceptions	2304	1288	439	676	2743	1727

NOTE: Females have more known conceptions than males because some breeding has occurred in multi-male groups where specific sires are unknown.

Table 3. Sample sizes for viable (liveborn) and nonviable (aborted or stillborn) offspring among 2,977 pigtail fetuses or infants with data appearing in the computerized records as of January 12, 1979.

	Viable		Nonviable		Total	
	Females	Males	Females	Males	Females	Males
Number	1218	1270	251	238	1469	1508
Per Cent of Total	41	43	8	8	49	51

This data base of 2,977 known conceptions among 1,037 breeders allows for calculation of normative pregnancy outcome and other breeding statistics under standard colony practices. The results of one such analysis are shown in Figure 1, presenting abortion, stillbirth, neonatal death, and neonatal survivor percentages for colony and wild born females. The wildborn data are broken down by weight at entry into the colony to assess effects of true maternal parity, as many wildborns are likely to have conceived before coming to the colony. Females entering under 4 kilograms are almost always immature, and as with colonyborn females their colony births are in the true order. Females entering between 4 and 5 kilograms may have had births in the wild, and those entering over this weight are almost certain to have had conceptions in the wild. Females entering the colony over 6 kilograms in body weight are usually older, and are likely to be at relatively high maternal parity after only a few years in the colony.

Besides serving as normative pregnancy outcome values, these data show two important effects. The first offspring of colonyborn females have almost 50% probability of dying in the first 30 days of life, although later births do not have an exceptionally high neonatal mortality. These females are very young-- comparable to 11-15 year old human girls. We are currently studying the causes of this phenomenon, which may be related to the problem of teenage pregnancy that is of current concern in this country. The high stillbirth value for older high parity wildborn females are also of great interest to us, as this phenomenon is also seen in older high parity women. Taken together, these two results suggest that at least some gross aspects of human pregnancy outcome epidemiology are replicated in this pigtail monkey colony. The percentages in figure 1 are relative to the number of animals having various numbers of prior conceptions. Table 4 presents these values from the current computerized records

# PREGNANCY OUTCOMES FOR PIGTAIL MONKEYS

-12-

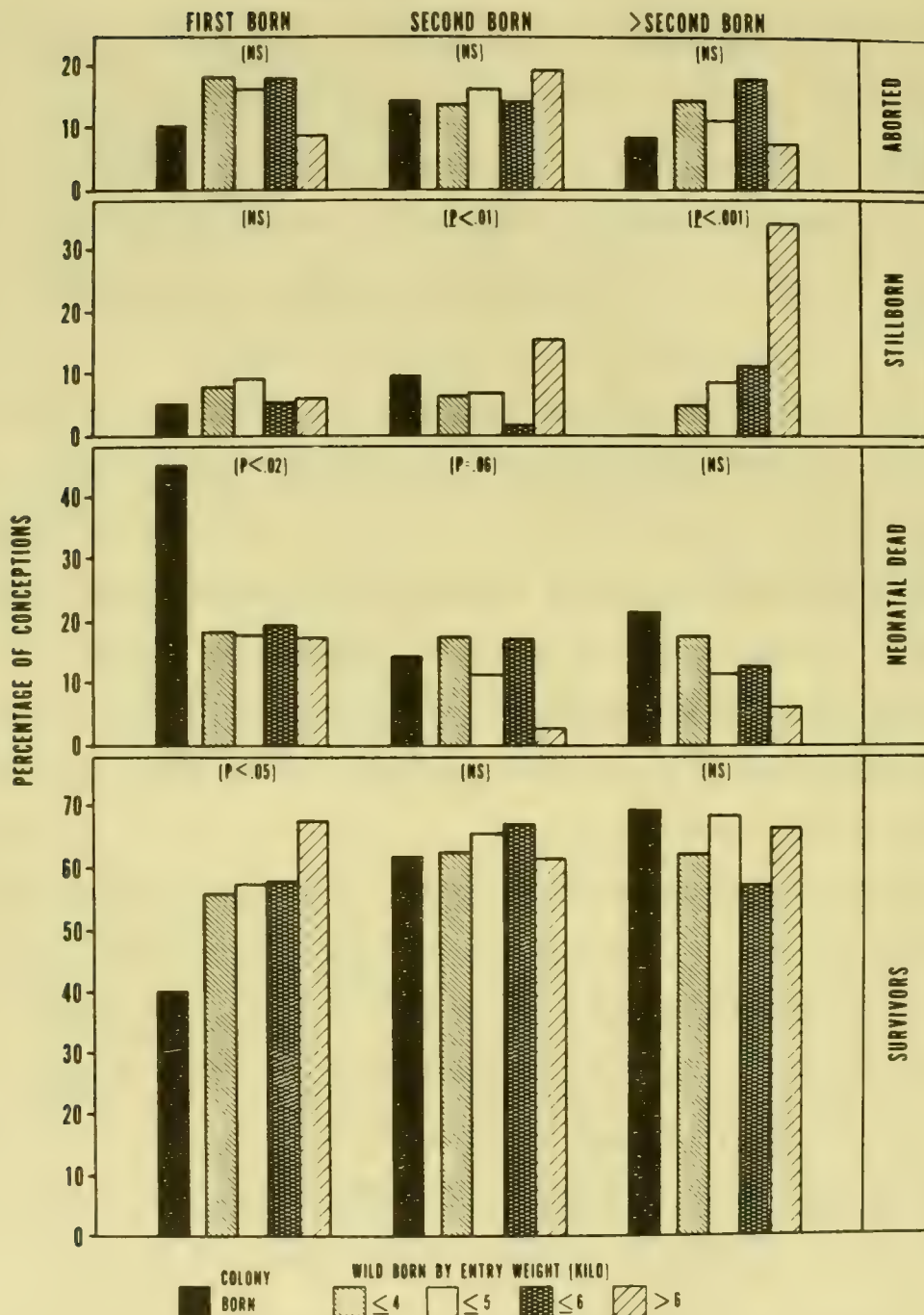


Figure 1. Pregnancy outcome distributions for Primate Center Breeding Colony colonyborn and wildborn pigtail macaques. Parentheses indicate the level of statistical significance between groups in each subset of conditions. Percentages are calculated within each birthorder and group, across the four pregnancy outcomes.



for wildborn and colonyborn females and males.

Table 4. Number of wild and colony born breeding age females and males with various frequencies of conceptions in the computer records as of January 12, 1979.

Number of Conceptions	Females		Number of Conceptions	Males	
	Wildborn	Colonyborn		Wildborn	Colonyborn
0	325	51	0	13	17
1	210	53	1-5	22	20
2	108	44	6-10	25	9
3	103	36	11-15	15	4
4	88	16	16-20	9	4
5	56	8	21-25	7	4
6	53	5	26-30	3	4
7	41	2	over 30	11	5
8	16	3			
over 8	21	2			

Analyses of birthweight and weight gain further illustrate the value and uses of computerized records. Figure 2 presents birthweight distributions for 820 viable male and 740 female newborns. Females are lighter than males, having a mean birthweight of 450 versus 490 grams (SD=78 and 81 respectively). Whether a particular individual is low in birthweight relative to all other newborns can be determined from this distribution. Our low birthweight criterion is the 10th centile; that value exceeded by 90% of the population (390 grams for males, 370 for females). Animals lighter than the 10th centile have a four times greater risk of natural death during postnatal days 1-30 than those born at any other 10 centile range. Also, as shown in figure 3, low birth weight monkeys of either sex reared under standard colony social group conditions remain in the lowest range of body weight through at least 4.5 years of age. This differs from humans, where low birthweight in itself does not predict especially light later weight, except for babies that are also immature at birth (small-for-dates). Differences in medical care and frequency of threat and physical attack-- which is often

directed by agemates toward smaller animals-- probably account for this discrepancy in growth between low birth weight humans and pigtail monkeys.

Figure 4 presents 6-year growth curves for colony-raised pigtails. Males are heavier than females throughout, and undergo a dramatic adolescent growth spurt at about the fourth year. We are reanalyzing these data now that more weights are available at older ages. The resulting curves on weights of over 1600 individuals should provide adequate normative expectations for body weight increase over age.

#### OTHER NORMATIVE AND DEVELOPMENTAL DATA

In addition to the data types described above, a number of additional measures characterizing pregnancy and offspring growth and physiology are available. Endocrine changes during the estrous cycle and pregnancy have been measured longitudinally on over 90 females (Schiller, Frederickson, Lewis, & Sackett, 1979). Over 580 pigtails have been screened for normative levels of cholesterol lipoproteins and triglyceride (McMahan, Rhyne, Lofland, & Sackett, 1979). The entire age-known pigtail colony has been assessed for developmental changes in gonadotropins (Faiman, Winters, & Sackett, 1979).

With respect to growth, a series of fetuses and in utero fetal x-rays provide norms for fetal development (e.g., Newell-Morris & Tarrant, 1978). A sample of these data is presented in figure 5, illustrating changes in fetal crown-rump length and appearance of foot and hand bone ossification centers in fetuses of known gestational age. Other data are available on changes in fetal skull dimensions and femur length. An important set of data for detecting birth defects is available on craniofacial and dental development from fetal stages to adulthood (e.g., Swindler & Tarrant, 1973). Several investigations have produced data on respiratory system development of fetuses and prematurely delivered infants (e.g., Woodrum, Hodson, & Guthrie, 1978). In addition to

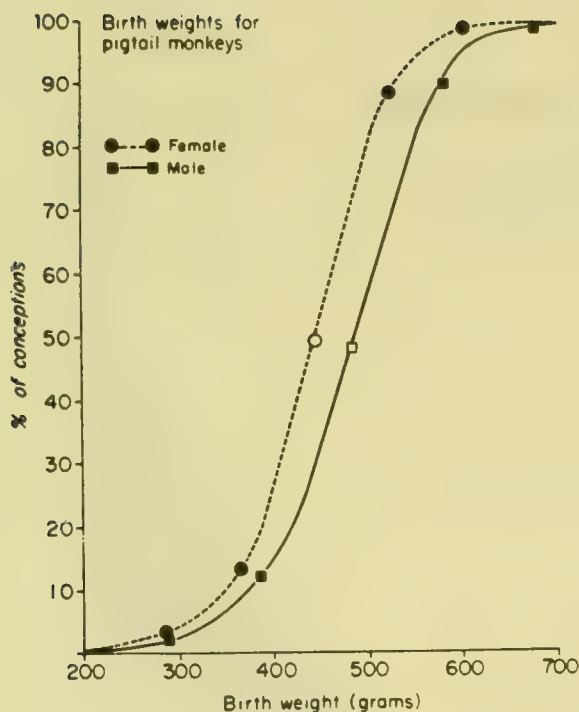


Figure 2. Birthweight distributions for male and female pigtail macaques. Solid symbols show 1 and 2 standard deviations from the means (open symbols)

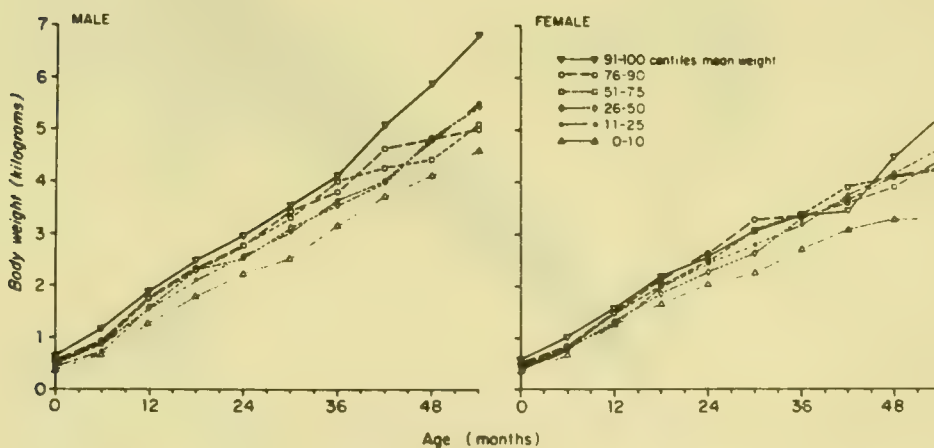


Figure 3. Body weight gains by male and female pigtail macaques as a function of the centile of body weight at birth. Among the six male birthweight centile groups, low birthweight males remain lightest and high birthweight males remain heaviest over this age span. Among females, only the low birthweight animals differ reliably from the other groups across the whole age range.

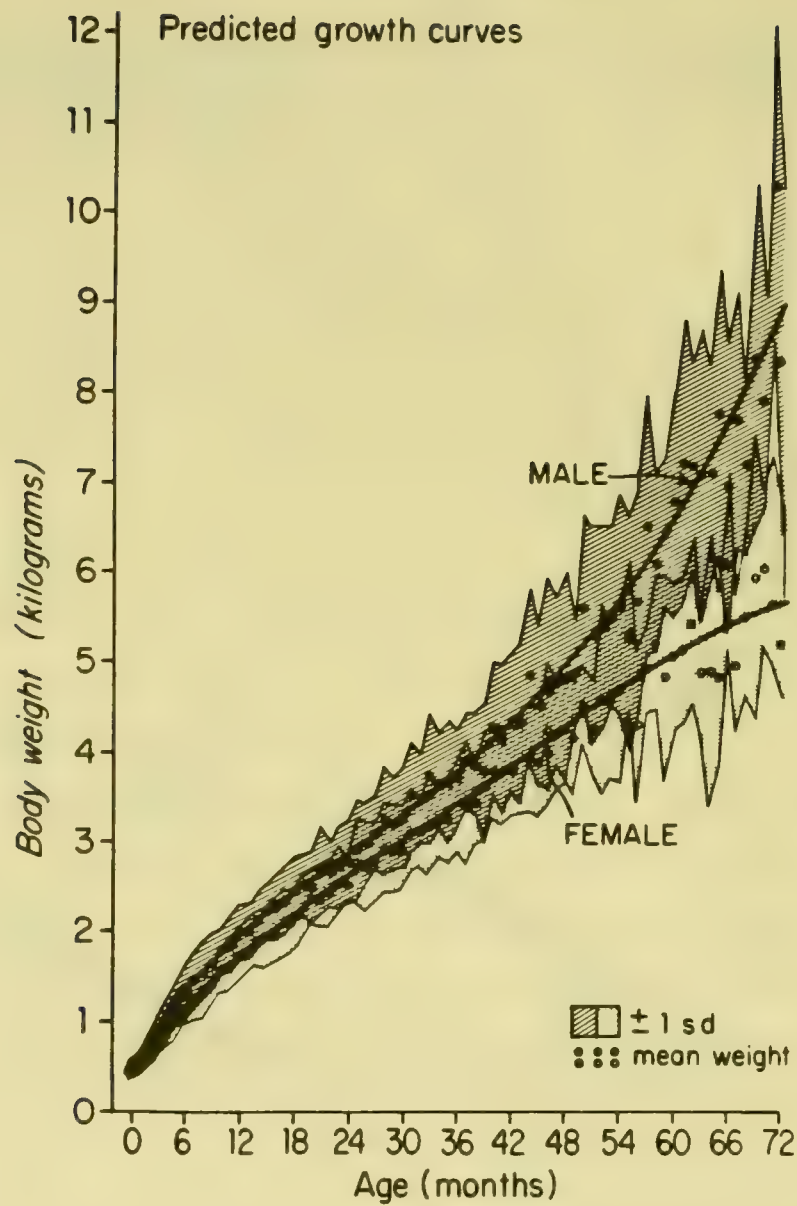


Figure 4. Growth curves for colony pigtailed macaques predicted by multiple regression from mixed longitudinal-crosssectional data including over 25,000 individual weight values.



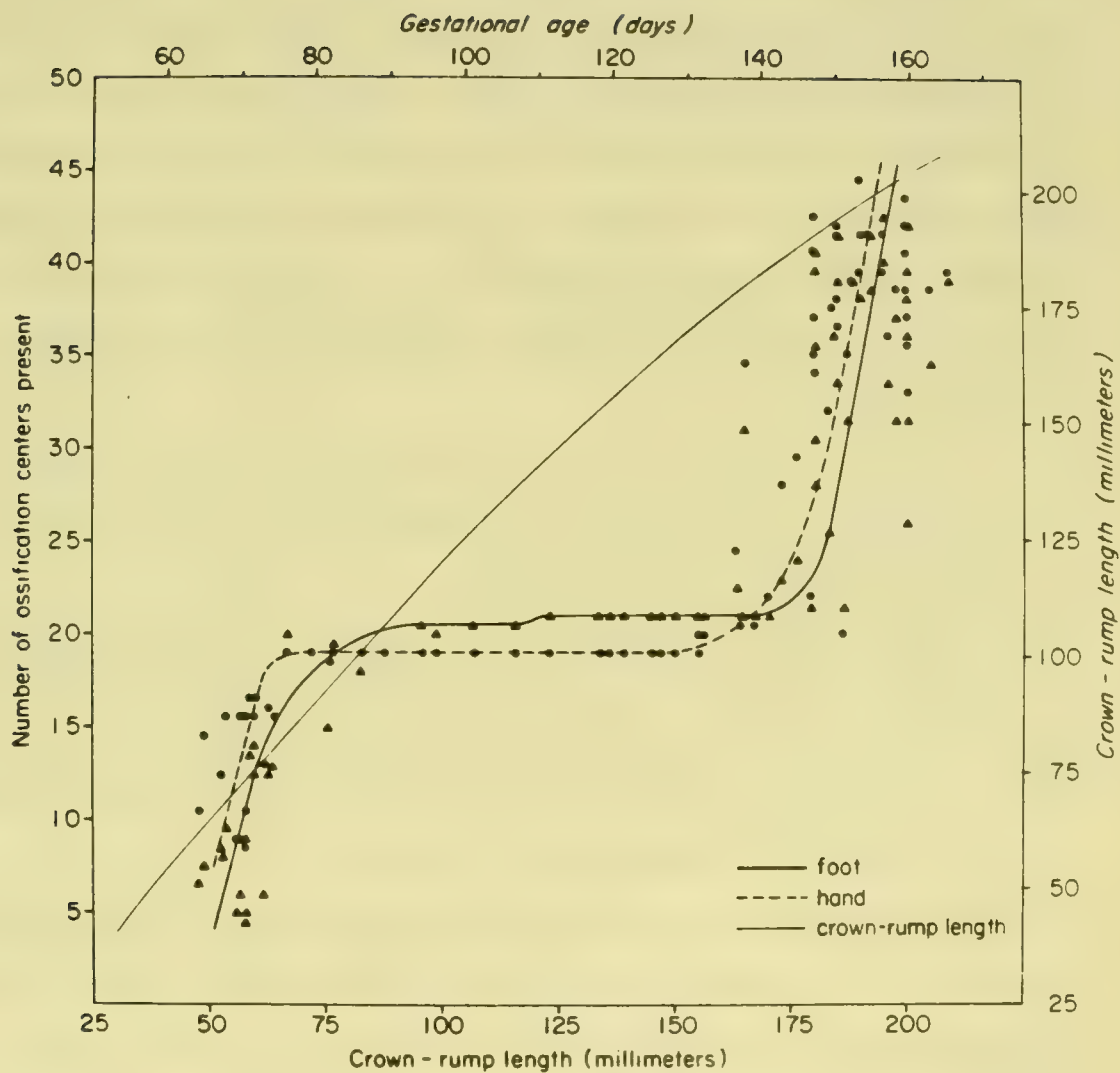


Figure 5. Prenatal norms for growth of fetal crown-rump length (curved solid line) over gestational age and for appearance of hand and foot bone ossification centers with increasing gestation.

hyaline membrane disease, these studies have uncovered several other respiratory problems similar or identical to those of human premature infants.

Fetal and placental morphology are currently under study at gestational ages of 45 days through birth. Brains from planned sacrifices and natural deaths of premature and full term pigtail newborns have been evaluated for abnormalities by light and electron microscopy (e.g., Sumi & Alvord, 1977). Along with necropsy information in the computerized records on aborted and stillborn fetuses, these data provide norms for fetal and placental development that can be used for assessing abnormalities of the products resulting from embryo transfer.

A final set of important normative information was produced in a recent study of pigtail macaque blood groups (Socha, Moor-Jankowski, & Sackett, 1978). Twenty specificities, based on human A-B-O blood groups and rhesus types, were found. A current study of natural pigtail antibodies should increase this number and produce pigtail-specific blood groupings. This information will allow matching or mis-matching of genetic variables in in vitro fertilization studies with pigtail ova and embryos.

Table 5, below, summarizes some, but not all, of the data types currently available for characterizing the course of pregnancy and fetal-infant growth in the Washington Regional Primate Research Center pigtail colony.

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Table 5. Major types of normative data and current samples sizes for characterizing estrous cyclicity, pregnancy, health, and offspring growth of Primate Center pigtail monkeys. Sample sizes are approximate as data are continuously added to most of these measurement sets.

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Parameter	Age range of individuals producing data	Sample Sizes	
Conception rates & Pregnancy Outcomes	3-20 years	1,037 breeders	2,977 conceptions
Cholesterol lipopro- teins & triglyceride	birth- 14 years	583 individuals	1,150 blood samples

(Table 5 continued)

LH and FSH	2 postnatal days-13 years	560 individuals	980 samples
Progesterone, ester- diol, cortisol, SBP	3-15 years	Detailed samples during estrous cycles: 140 individuals    1,500 samples	
		Longitudinal samples during pregnancy: 95 individuals    2,000 samples	
Pigtail blood groups	1-15 years	180 individuals	300 blood samples
Hematology & blood chemistry (20 variables)	Prenatal	50 fetuses & 80 placentas	
	Birth-20 years	3,000 individuals	15,000 samples
Clinical Treatments	Birth-20 years	1,800 individuals	5,000 treatments
Pathology reports from necropsy	Fetus-20 years	1,600 individuals	
Birthweight & weight gains of age-known animals	Birth-14 years	1,680 individuals	45,000 values
		Longitudinal data during infancy: 425 infants    10,000 values	
Bone ossification,femur length, skull dimension	60 gestational days-postnatal 9 months	240 fetuses	380 measures
		120 infants	1,200 measures
Fetal & placental morphology	45 gestational days-birth	Tissue from gestation age-known C-sections: 110 specimens	
		Tissue from natural deaths: 300 specimens	
Fetal & infant brain tissue	45 gestational days-14 post- natal months	From age-known individuals in experi- mental studies: 80 individuals	
		From natural deaths: 300 specimens	
Fetuses & newborns in lung studies	120 gestational days-birth	From experimental studies of age-known individuals: 100 specimens	
		From naturally occurring deaths: 300 specimens	
Craniofacial & dental development	60 gestational days-10 years	200 individuals	2,000 samples

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#### HIGH RISK BREEDER POPULATION

In most primate colonies unproductive or constantly sick breeders are eliminated from the population. In our colony such breeders are under study

for causes of bad pregnancy outcomes and behavioral, physiological, and anatomical development of surviving offspring (NICHD program project grant HD-08633; Prematurity in Primates: Causes, Effects, Prevention; G. Sackett, Principle Investigator; 24 current collaborating scientists). The project has 45 female and 5 male high risk breeders and 32 female and 4 male low risk monkeys. These animals are a unique resource to study in vitro fertilization and embryo transfer for both clinical and fundamental knowledge. The rationale for this statement includes (i) the fact that five years of reproductive biology data are already available on these animals, (ii) the high risk breeders and other females in the general colony have the same range of abnormalities as those leading human women to the embryo transfer procedure, and (iii) detailed norms concerning past pregnancy outcomes and offspring development of these specific individuals have already been gathered under standardized conditions of mating and offspring rearing.

High risk breeders are defined in terms of excess abortions, stillbirths, and neonatally dead or low birthweight offspring. Table 6 illustrates these characteristics for females who produced three or more conceptions under standard harem group conditions. Table 7 gives data for males. As seen in these tables, high risk females and males greatly exceed other monkeys in producing fetal and neonatal loss and developmentally at-risk low birthweight offspring. The male results are surprising, as their matings were with a random assortment of females. Pigtail males thus appear to contribute to bad outcomes independently of particular female factors-- a phenomenon almost completely unstudied in humans. The data for these tables came from breeders prior to 1974. Since that time some of the original animals have been lost or dropped from the project. However, 5-10 new high risk females and 1-2 high risk males are identified from among general colony members each year.



Table 6. Pregnancy outcomes of high, low, and intermediate risk multiparous females prior to experimental mating on the Prematurity in Primates project.

Risk Condition	Measure	Pregnancy Outcome				Low Birth	
		Viable	Aborted	Stillborn	Neonatal Dead	Total	Weight
HIGH (N=37)	N conceptions	66	51	38	30	185	62
	Mean/breeder	1.8	1.4	1.0	0.8	5.0	1.7
	% of total	35.7	27.6	20.5	16.2		33.5
LOW (N=29)	N conceptions	150	6	1	4	161	6
	Mean/breeder	5.2	0.2	0.0	0.1	5.6	0.2
	% of total	93.2	3.7	0.6	2.5		3.7
INTERMEDIATE (N=110)	N conceptions	376	86	54	54	570	58
	Mean/breeder	3.4	0.8	0.5	0.5	5.2	0.5
	% of total	66.0	15.1	9.5	9.5		10.0

Table 7. Pregnancy outcomes sired by high and low risk males prior to experimental mating on the Prematurity in Primates project.

Risk Condition	Measure	Pregnancy Outcome				Low Birth	
		Viable	Aborted	Stillborn	Neonatal Dead	Total	Weight
HIGH (N=3)	N conceptions	28	28	16	25	97	25
	Mean/breeder	9.3	9.3	5.3	8.3	32.3	8.3
	% of total	28.9	28.9	16.5	25.8		25.8
LOW (N=3)	N conceptions	73	12	5	8	98	5
	Mean/breeder	24.3	4.0	1.7	2.7	32.7	1.7
	% of total	74.5	12.2	5.1	8.2		5.1

Males and females were time mated within risk conditions over a three year period to compare pregnancy outcomes and development of surviving offspring. Each female had two pregnancies; one under minimal prenatal stress and another under high stress produced by daily hand-capture (Sackett & Holm, 1978). High risk females under high or low stress produced 55% abortions, a significant increase over their prior 28% abortion rate. Under low stress, low risk females had 5% abortions, exactly as expected from their prior rate. When stressed,

the low risk abortion rate increased to 30%. These results validated the basic risk conditions under experimental treatment, and suggested that prenatal stress may affect only low risk females.

Compared with low risk offspring, high risk survivors exhibited a number of developmental deficits. These included lower birthweight and immature skeletal systems for gestational age (Fahrenbruch, Burbacher, & Sackett, 1979a), a number of placental abnormalities (Fahrenbruch, Burbacher, & Sackett, 1979b), slower postnatal weight gain (Sackett, Holm, & Fahrenbruch, 1979), and much increased time to develop diurnal cycles of heart rate, respiration, temperature, and sleep-wakefulness patterns (Sackett, 1979). Each of these effects was most deviant for offspring of high risk females who were stressed during pregnancy. Offspring of stressed females were also deficient in a number of standard primate learning tests, although these data are not yet completely collected and analyzed. Preliminary analyses of other tests measuring neonatal reflex development, exploratory behavior, and social interactions with agemates suggest that maternal risk and prenatal stress may also affect other behavioral dimensions.

A major part of our current research is to identify and correct causes of abortion in individual high risk females to produce surviving offspring for developmental study. Many preconception, genetic, and prenatal variables may underlie high risk. This is the area where embryo transfer, as a research tool, can greatly improve our research effort. Males may contribute to bad pregnancy outcomes via their behavior before and during mating-- a stress source known to affect pregnancy in rodents (Joffee, 1965). Comparing conceptions produced by in vitro and natural fertilization yields direct assessment of stress and other preconception and mating factors on pregnancy outcome and offspring development. Using embryo transfer to crossfoster ova between high and low risk

females leads to direct pinpointing of genetic versus prenatal factors as causes of bad pregnancy outcomes. Candidly, the development of prenatal crossfostering as a research tool is my primary motivation for interest in embryo transfer and in preparing this paper.

#### NEWBORN AND INFANT DEVELOPMENTAL MEASURES

The Infant Primate Research Laboratory has developmental measures on 486 pigtail newborns and infants. These animals were all removed from their mothers at, or shortly after, birth. They were reared in a nursery under standard handling and feeding conditions (Ruppenthal & Reese, 1979). Some animals were completely normal at and after birth. Others were sick, premature, low in birth weight, maternally rejected, or traumatized physically. A third set were subjects in manipulative experiments involving premature or full term C-section delivery, other medical interventions, or experimental rearing involving social or perceptual deprivation. The developmental measures assess anatomical, physiological, and behavioral factors. Norms for most tests are available for at least 50 healthy controls, as well as over 100 monkeys known to be developmentally deficient or retarded in some important way. The standard test schedule and current sample sizes for each measure are given in table 8.

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Table 8. Schedule of standard tests and measurements on pigtails during the neonatal and infancy periods, and number of animals tested to date.

TEST	AGE AT ASSESSMENT	SAMPLE SIZE
Simian Apgar	day 1 & 2	over 250
Bone X-Rays & body size	day 1, 14, 28 week 6, 12, 16, 20, 32	311
Tooth Eruption	daily, weeks 1-24	150
Body Weight	daily, month 1 3/week months 2-3 weekly, months 4-12	486
Diurnal Cycles	daily once per.5-4 hours, weeks 1-4	325

(Table 8 continued)

Blood Draws	1cc days 1-5 4cc weeks 8, 16, 24 10cc week 32	over 225
Respiration & Autonomic Function	day 1-5 3 times week 2 2 times weeks 3-7 daily weeks 8-12	15
Sucking Reflex	day 1-14 2 times weeks 3-4 1/week 5-10	over 200
Startle Reflex & Orienting	2 times/week 1-5 1/week 6-24	over 200
Clasp-Grasp Reflexes	2 times/week 1-4 1/week 5-6	over 200
Neurological Reflexes	daily weeks 1-8	over 250
Home Cage Behavior Inventory	2 times per week from birth to 12 months	over 450
Playroom Social Interaction	3 times per week from weeks 5-month 12	over 450
Learning Test Series	daily weeks 16-32	over 150
Social Preferences	Mothers: Neonate versus adult female day 1, 3, 7 Offspring: 1 time per month 2-9	over 150 over 200

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HEALTH AND GROWTH. A simian apgar, like that used with humans, rates newborns for health status and reactivity. Bone x-rays, anthropometric measures, dental eruption dates, and body weight gain measure growth. Blood draws are taken to measure nutritional parameters such as amino acid spectrum, iron, and vitamin levels. Bloods also yield measures of sex hormones and cortisol. Cycles of sleep-wakefulness are measured by observing newborns once per 30 minutes, 24-hours each day, for sleep, inactive waking, or active arousal. Every four hours respiration, heart rate, and rectal temperature are also measured. These basic life functions become cyclic by day 7 in normal newborns. Low birth weight, sick, and respiratory distressed monkeys take much longer to develop cyclicality. This test battery yields sensitive, quantitative, health and maturity indices for developing monkeys.



BASIC REFLEXES. Neurological reflexes similar to those assessed in human pediatrics are routinely rated for all nursery newborns. Three behavioral reflexes related to major survival skills needed by newborn monkeys are also measured. (i) Each neonate receives one daily feeding from a nipple connected to a pressure sensing instrument (Kron, Ipsen, & Goddard, 1968) measuring rate, amplitude, and burst-pause distributions during sucking. (ii) Clasping and grasping reflexes are studied in a 'baby-spin' apparatus (Castell & Sackett, 1973). The infant clings to a blood pressure type cuff while being rotated by a motor through two head-forward circles. Pressure transducers quantify clasp-grasp strength at various rotation angles (e.g., head down, sideways, head up). The angles eliciting maximum pressure change systematically over the first month, a change that indexes neural-motor maturation. (iii) Infants are placed in a chamber containing siesmographic detectors in the floor. A brief air puff, white noise, pure tone, or light flash is presented in a random order, along with no-stimulation control trials. Time to jump and amount of motor activity following each stimulus measures sensory-motor maturity and central nervous system reactivity. These three reflex tests are controlled by a computer, which also collects and summarizes the primary voltage data in a digital form.

Another test series, conducted to date on only a few neonates, uses radio telemetry transmitters to measure heart rate and respiration changes to repetitive sounds. This tests habituation of the autonomic nervous system, a commonly used way of assessing autonomic maturity. The protocol also tests the 'dive' reflex, measuring ability to recover from a long period without breathing (apnea), a problem common in the human sudden-infant-death syndrome.

PERSONAL AND SOCIAL BEHAVIOR. Two tests study infant behavior in home

cages and during social interactions with agemates in a playroom. Humans observe these behaviors using standard catalogues of monkey response categories, entering numbers coding specific activities into a keyboard connected to a computer (Sackett, Stephenson, & Ruppenthal, 1973). Frequency and duration of behaviors such as play, exploration, fear-withdrawal, and aggression are measured from these records. Sequential relationships between behaviors of interacting infants, amount of initiation versus receiving of interactions, and the amount of self-directed activity are also measured (Sackett, Holm, Crowley, & Henkins, 1979).

A multiple choice preference test measures attractiveness of neonates to postpartum females as an index of maternal motivation (Sackett & Ruppenthal, 1974). Social motivation of infants is assessed in their choices among adult females versus males, own versus opposite sex agemates, and familiar versus unfamiliar animals. Changes in these preferences occur systematically during infancy, and are useful for both assessing social maturity and for interpreting causes of playroom social behavior abnormalities (Sackett, 1972). We are thoroughly familiar with abnormal behaviors produced by rearing infant macaques in social-perceptual deprivation conditions, and can detect such abnormalities in both quantitative and qualitative form in pigtail monkeys (e.g., Sackett, Holm, & Ruppenthal, 1976).

LEARNING. A standard battery of learning tests on our pigtail infants includes (i) adaptation to a discrimination learning apparatus, (ii) simple two-choice black-white discrimination habits for food reward followed by a reversal learning in which the previously unreward color is correct, (iii) learning a sequential series of responses followed by a change to a single response to obtain a reward (set breaking behavior), and (iv) learning set formation (Harlow, 1959). In the last task, the infant is presented with two

objects, one of which covers a hidden reward. The same objects appear for six trials in a row, then a new object set is used. If the animal displaces the correct object it receives a raisin or piece of grape. Incorrect responses yield nothing. The monkey's job is to learn that correct responses should be followed by continued choice of that object, while incorrect responses should be followed by choice of the other object (a win-stay, lose-shift learning set). This difficult concept for both infant monkeys and humans has been used as a comparative test of intelligence for a number of animal species, and for normal and retarded humans.

OTHER MEASURES. Several other tests developed for our pigtail monkeys include (i) assessment of visual acuity and color vision (Boothe, Teller, & Sackett, 1975), (ii) measurement of peripheral nerve conduction velocity to index nervous system maturity (Spelman, Holm, & Sackett, 1979), (iii) operant response procedures measuring performance as early as three days of age (Sackett, Tripp, Milbrath, Gluck, & Pick, 1971), and (iv) a recently developed method for studying the way in which infants search for hidden objects. The latter is similar to Piagetian methods for studying cognitive-memory maturation in human infants.

The final type of procedure available in the Infant Laboratory concerns measurements at the time of labor and delivery. Three delivery teams are on call on different nights, as almost all pigtail births occur at night. Pregnant females are observed at least once per 30 minutes, 24-hours each day, for visual signs of labor. These include clear postural and motor activity changes unique to labor. The labor and delivery are recorded on video tape for analysis of behavior, contractions, and the actual birth process. The delivery team separates the mother and infant and performs a number of measurements, collects tissues and blood for anatomical and pathological study,

and recovers and processes the placenta for various measurements and analyses. Over 150 births have occurred in the laboratory, with detailed measurements available on the course of labor and delivery for 80 animals.

In summary, 15 standard tests are available for assessing growth, physiological-behavioral maturity, learning, and social-personal behavior. Detailed norms exist on these tests for pigtail infants reared under standard and controlled environmental, social, and nutritional conditions. Other tests are available for measuring perceptual and intellectual development, although more norms are required before these can be applied to the problem of detecting abnormalities. Lastly, methods and normative data are available concerning the course of labor and delivery-- an area of special importance for studying maternal abnormalities following embryo transfer.

#### RESEARCH PLAN

This section presents a five year proposal to determine whether in vitro fertilization and embryo transfer produce abnormalities in pregnant, fetal, and/or infant pigtail macaques. The first two years involve method development and personnel training. The latter three years produce offspring for experimental studies.

#### METHOD DEVELOPMENT AND PERSONNEL TRAINING

The current success rate in producing primate fetuses by embryo transfer is, at best, 1 in 100 attempts. This must be raised to 5-10 per 100 before a primate model is practical. Under timed mating pigtail females become pregnant after 2.5 successive matings (Anderson & Erwin, 1975). This yields an estimate of 60% spontaneous ova or embryo loss, a value typical for many mammalian species (Biggers, 1978b). Steps proposed to achieve a 10% success rate form the first two years of the research effort.

RECOVERY OF OVA. Time of ovulation can be detected with reasonable



accuracy in pigtaills by observing perineal swelling detumescence. Ova will be recovered from females at this stage using laparoscopy to visualize the ovary (e.g., Dukelow & Ariga, 1976) and to position a catheter to flush and recover ova from the oviduct (e.g., Kuehl & Dukelow, 1975). These capture methods have been successful with baboons, squirrel monkeys, and macaques. We successfully recovered a pigtail ova on the first try, under the direction of Drs. James Kraemer and Richard Dukelow. Continuing efforts should give us an estimate of actual recovery percentage in 3-4 months. Using females known to have just ovulated, ova recovery should reach 70-90 %. The basic laparoscopy procedure has been used in our colony for years (e.g., Blakley, Blaine, & Morton, 1977), and some females have had the procedure over 50 times with no detectable effects on future ovulation or fertility.

We are also developing instruments for recovery of fertilized ova. This has been done in macaques and baboons (e.g., Hurst, Jeffries, Eckstein, & Wheeler, 1976), but is difficult in macaques due to a highly curved cervix. Anatomical and engineering studies are in progress to produce an instrument and technique for passing through the pigtail cervix. This work will include studies using ultrasound to visualize the uterus and radio-opaque dyes and deposit of surrogate-ova microspheres to mimic embryo transfers. Once developed, 3-6 months will be required to train technical personnel on these procedures. This period of method development and training should take about 12 months.

IN VITRO FERTILIZATION AND OVA CULTURE. This area is probably the most difficult on the project. It requires capture of sperm from male donors, fertilization of fresh ova, and in vitro ova culture for 4-5 days. Success of the culture depends critically on proper environmental and chemical factors. Sperm collection by electroejaculation is a standard practice in primate husbandry

(e.g., Thompson, 1978; Fordney-Settlage & Hendrickx, 1974). It has been used with success in our colony, and we have developed a stimulator producing ejaculation with low current levels at short application durations. This work, and cervix studies, will proceed in collaboration with Dr. Richard Blandau, an expert in the primate cervix and in fertilization.

Procedures for in vitro fertilization and culture have been developed by several investigators for primate materials (e.g., review by Biggers, 1978b). We will use this information and the assistance of Dr. Roger Donahue to develop and test a method for fertilization and culture of pigtail ova. Dr. Donahue is an expert in embryo development, who worked with Dr. Edwards in earlier work on in vitro fertilization. This work may take 12-18 months, and will proceed simultaneously with ova recovery and transfer development. This work aims to both produce cultures and to assess normalcy of the embryos during the preimplantation stages.

EMBRYO TRANSFER VALIDATION. The final developmental phase will use 30 mature pigtail females with histories of good pregnancy outcomes and regular estrous cycles. Fifteen animals (autotransfer group) will have their own embryos transferred after 4-5 days of in vitro culture. Another 15 animals (crosstransfer group) will be recipients of in vitro fertilized and cultured embryos from a different female. Crosstransfer subjects will be chosen on the basis of estrous synchrony from among the several hundred potential available animals. Synchrony will be estimated from perineal swelling, and confirmed by laparoscopy and hormone measurements. Results from repeated attempts to transfer embryos will estimate percentage of successful implantations and actual pregnancies. We have norms for hormone changes in early pigtail pregnancy and experience with the NIH HCG pregnancy detection kit. These data suggest that pregnancy can be confirmed by 17-20 days after conception with over 95% accuracy. If a 10%

or greater success rate is achieved we will proceed to the main experiments. If this success rate is not met, further work will be done on transferred embryos recovered surgically after implantation to determine the causes of transferred embryo loss. This developmental work will proceed in collaboration with Dr. Thomas Shepard, an expert in human and primate embryology.

In summary, we believe that successful procedures for ova capture, in vitro fertilization and culture, embryo transfer, and validation of a 10% fetus production rate can be accomplished with pigtail macaques in a two year period. Some work is already in progress, but most of the effort will require more funds for personnel and equipment than currently available. A proposed budget and personnel for this developmental phase is given after the next section outlining experiments to detect abnormalities.

#### ASSESSMENT OF ABNORMALITIES IN THE PRODUCTS OF EMBRYO TRANSFER

Thirty females with a history of good pregnancy outcomes, regular estrous cycles, and previous offspring having detailed growth and behavior norms will be subjects. Some of these will come from animals used to determine embryo transfer success rates, and may have already produced an embryo transfer offspring. Such offspring will have been studied in the same ways as those produced in this experiment.

Each subject will have two in vitro fertilization and embryo transfer pregnancies. One will be an autotransfer, the other a crosstransfer, with order random. Pregnancies will proceed in single cage housing under minimal stress. Two sires with histories of good pregnancy outcomes will be sperm donors to half of the total fertilized ova. For each pair of ova donors and recipients the same sire will fertilize both the auto and cross transfer ova.

Hormone and behavior measures will be taken during pregnancy, as well as fetal x-rays and amniocentesis to study fetal growth and chromosomes. Pigtail chromosomes have been well described (e.g., Chiarelli, 1973), and any gross



abnormalities should be detectable. Labor and delivery of each pregnancy will be observed, and blood and the placenta and other tissues collected for analysis of abnormalities. Infants will be separated permanently from mothers immediately after birth, and reared under standard Infant Laboratory conditions. All regular scheduled measures will be taken (table 8), and offspring will also be tested for intellectual development using the object permanence procedure. Spontaneous deaths will be studied for anatomical abnormalities, and individuals exhibiting gross behavioral or physiological abnormalities will be sacrificed at 12 month of age for detailed pathological study.

It will average ten monthly attempts to produce each pregnancy with a 10% success rate. Coupling this with a 5.5 month gestation period, we should produce nearly 30 offspring in 12 months and the total 60 in two years. Postnatal studies will take 12 months, so the entire experiment should be ended in three years.

Analysis of computer records suggest that birth defects occur in about 0.5% of conceptions in our pigtail colony. With 60 offspring and no effects of embryo transfer on birth defect risks we should see no more than one clear birth defect. The occurrence of just several birth defects would constitute statistical evidence for increased risk with this sample size. Statistical comparisons of other pregnancy, labor, delivery, and offspring development variables will analyze differences between auto and cross transfers and will compare embryo transfer products with the norms described in the previous section of this paper. With 60 experimental pregnancies and offspring and norms on upwards of several thousand individuals on some measures we should be able to detect all but the most subtle abnormalities -- if they indeed exist.

COMPARISON OF IN VITRO WITH IN VIVO FERTILIZATION. This study will be run in years 4-5 if abnormalities occur in experiment 1. The purpose is to determine whether pre or post implantation factors produce embryo transfer



abnormalities. Experimental subjects will be females who produce abnormal fetuses or infants. Controls will be females who produce no abnormal offspring by embryo transfer. Each experimental female will receive two pregnancies by auto or cross transfer, depending on which condition resulted in her abnormal offspring. A control female will be matched with each experimental subject for her treatment. On one pregnancy, naturally fertilized ova will be recovered from the uterus prior to implantation. These will be either reintroduced to that female, or transferred to the matched pairmate. A subsequent pregnancy will use the in vitro procedure producing the original abnormality in an attempt to replicate the original effect. All other pregnancy, labor, delivery, and offspring conditions will be identical to experiment 1. Sample sizes will depend on the number of abnormal offspring found in experiment 1. It seems unlikely that this would exceed 10 experimental and 10 control females.

#### AUTOTRANSFER AND PRENATAL CROSSFOSTERING WITH REPRODUCTIVELY ABNORMAL FEMALES.

As previously described, a number of our pigtail females habitually produce bad pregnancy outcomes or fail to conceive. Some conception failures are caused by tubal blockage, aging with irregular estrous cycles, or hormone deficits. These abnormal animals present many of the conditions found in women seeking embryo transfers, and are the most likely monkey candidates to produce abnormal offspring. Many of these monkeys have already produced 3-4 offspring reared under standard conditions with available developmental measurements. Females from these abnormal groups will be subjects, paired with controls from the breeders at low risk for bad pregnancy outcomes.

Subjects with tubal blockage will receive an auto and a cross transfer from a normal female. Females at high risk for bad pregnancy outcomes and those with hormonal or other infertility problems will receive an in vitro fertilized embryo from a normal female and will donate an embryo to the

normal partner as recipient. All pregnancies and offspring will be studied under the same procedures described for experiment 1. It is likely that subgroups will contain 10-12 females with tubal blockage, 10-12 with hormonal or aging problems, and 20-25 at high risk for bad pregnancy outcomes.

When compared with results of experiment 1, these studies will determine (i) abnormality rates when embryos from abnormal females are carried by normal individuals, (ii) the extent to which a history of bad pregnancy outcomes is due to genetic versus prenatal causes, and (iii) the success of females with tubal blockage in maintaining pregnancy and producing normal offspring as recipients of their own embryos and embryos from normal females.

These studies are by no means exhaustive. Two, out of many, other important questions concern (i) effects of hormone treatments to produce ova for auto and cross embryo transfer, and (ii) effects of prenatal stress on normal and reproductively deviant recipients of embryo transfers. Such studies, though not specifically planned here, would likely follow completion of the three planned studies even if abnormalities were not produced.

HYPOTHESES. Most of the questions to be answered in these experiments are largely empirical-- that is, there are few theoretical reasons to expect increased incidence of specific abnormalities in embryo transfers reaching fetal stages. However, a few predictions do seem reasonable. (1) A greater incidence of abnormalities should occur after crosstransfer than following autotransfer due to incompatibilities between donor and recipients in immune and other genetic mechanisms. (ii) More abnormalities should occur following in vitro than in vivo fertilization due to disease or contamination of a subtle nature during the in vitro period. Expected differences are, however, small because most abnormal embryos should be lost early in pregnancy according to data on nonprimate mammalian species. (iii) Females with reproductive abnormalities or a history of bad pregnancy outcomes will have a higher

incidence of abnormalities following embryo transfer than reproductively normal females. This is expected on the basis of our work with females at high risk for bad outcomes, and is perhaps the most important aspect of this research as a primate model of the human condition.

#### RATIONALE FOR REARING WITHOUT MOTHERS.

In these studies infants will be removed from their mothers at birth. This is proposed for two reasons. First, if embryo transfer produces postnatal maternal abnormalities, these defects rather than infant characteristics could be responsible for offspring abnormalities. Removing the mother removes postnatal maternal variables as potential causes of abnormality. Second, nursery rearing more closely approximates human infant rearing conditions in this country than rearing by monkey mothers. Nursery infants are fed from a bottle and receive a great deal of physical contact from human mother-surrogates. Of great importance, they receive a standard formula diet. If the question of postnatal maternal factors becomes important in the future, it can be studied in pigtail monkeys. We are currently conducting experiments in which 40-50 mother-reared infants will be studied over the next 2-3 years. Postnatal maternal factors following embryo transfer could be compared with these natural pregnancies after this time.

#### BUDGET AND PERSONNEL

A reasonably precise estimate of cost for this five year research project is presented next. Estimates are based on (i) current Primate Center charges for animals and per diem maintenance expense, (ii) current salaries for each personnel category plus 5% yearly increases, and (iii) experience with personnel, supplies, equipment, and outside services necessary on the Prematurity In Primates project. The tables below present this budget in the format required for an NIH program project research grant.

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PERSONNEL Salary (% effort)

	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5	TOTAL
Breeding - Embryo Transfer						
Veterinary Tech	22,000(100)	23,100(100)	24,250(100)	25,500(100)	26,800(100)	121,650
Animal Tech	18,000(100)	18,900(100)	19,850(100)	20,850(100)	21,900(100)	99,500
Laboratory Tech	8,000(50)	8,400(50)	8,800(50)	9,250(50)	9,700(50)	44,150
Embryologist	30,000(100)	31,500(100)	16,600(50)	8,750(25)	9,200(25)	96,050
Students (Hourly)	10,000	12,000	12,000	12,000	10,000	56,000
Total	88,000	93,900	81,500	76,350	77,600	417,350

Infant Laboratory

Research Assoc.	20,000(100)	21,000(100)	22,050(100)	23,150(100)	24,300(100)	110,500
Laboratory Tech	----	6,500(50)	13,650(100)	14,350(100)	15,100(100)	49,600
Laboratory Tech	----	6,500(50)	13,650(100)	14,350(100)	15,100(100)	49,600
Laboratory Tech	----	6,500(50)	13,650(100)	14,350(100)	15,100(100)	49,600
Students (Hourly)	----	4,000	10,000	15,000	15,000	44,000
Total	20,000	44,500	73,000	81,200	84,600	303,300

Fetal-Placenta Morphology Tech	----	8,400(50)	8,800(50)	13,860(75)	14,550(75)	45,610
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Cytogenetics Tech	----	4,200(25)	4,400(25)	4,625(25)	4,850(25)	18,075
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Endocrinology Research Tech	18,000(100)	18,900(100)	19,850(100)	20,850(100)	21,900(100)	99,500
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TOTAL PERSONNEL	126,000	169,900	187,550	196,885	203,500	\$883,835
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EQUIPMENT	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5	TOTAL
Cell Culture Lab & Replacement Parts for breeding apparatus	40,000	5,000	2,500	2,500	2,500	52,500
TV Monitoring Items for Labor-Delivery, Behavior Testing & ReplacementParts	----	10,000	2,000	2,000	2,000	16,000
Floppy Disk for Computer	----	5,000	----	----	----	5,000
Timed Mating & Labor-Delivery Cages	10,000	10,000	----	----	----	20,000
Total Equipment	50,000	30,000	4,500	4,500	4,500	93,500

#### SUPPLIES

Breeding & Embryo Transfer	10,000	10,000	10,000	5,000	5,000	40,000
Infant Laboratory	----	1,000	3,000	5,000	5,000	14,000
Placanta-Fetal Morphology	1,000	1,500	2,000	2,500	2,500	9,500
Endocrinology	2,000	2,000	3,000	3,000	3,000	13,000
Cytogenetics	1,000	1,000	1,500	1,500	1,500	6,500
Data Analysis	200	300	500	1,000	1,000	3,000
Total Supplies	14,200	15,800	20,000	18,000	18,000	86,000

#### ANIMAL ACQUISITION (Number) cost

Breeders(\$310/@)	(34)10,540	(22)6,820	(31)9,610	(31)9,610	(21)6,510	43,090
Infants(\$210/@)	----	( 5)2,280	(30)13,700	(35)15,900	(45)20,500	52,380
Total Animal Acquisition	10,540	8,920	15,910	16,960	14,910	67,240

#### ANIMAL PER DIEM (Animals/day) cost

Breeders(\$1/day)	(34)12,410	(34)12,410	(45)16,425	(50)18,250	(40)14,600	74,095
Infants(\$1.25/day)	----	( 5) 2,280	(30)13,700	(35)15,900	(45)20,500	52,380
Total Per Diem	12,410	14,690	30,125	34,150	35,100	126,475

CONTRACTED SERVICES	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5	TOTAL
Neuropathology	----	2,000	3,000	5,000	10,000	20,000
Virus Laboratory	2,000	2,000	2,000	2,000	2,000	10,000
Blood Typing	3,000	1,000	3,000	2,000	2,000	11,000
Computer (U. Wash.)	1,000	1,000	1,500	2,000	2,000	7,500
Total Services	6,000	6,000	9,500	11,000	16,000	48,500

TOTALS FOR ALL CATEGORIES IN ALL YEARS

CATEGORY	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5	TOTAL
Personnel	126,000	169,900	187,550	196,885	203,500	883,835
Animal Acquisition	10,540	8,920	15,910	16,960	14,910	67,240
Animal Per Diem	12,410	14,690	30,125	34,150	35,100	126,475
Supplies	14,200	15,800	20,000	18,000	18,000	86,000
Equipment	50,000	30,000	4,500	4,500	4,500	93,500
Services	6,000	6,000	9,500	11,000	16,000	48,500
Travel to Breeding Colony & Seattle	1,200	1,500	2,500	2,500	2,500	10,200
Total all items	220,350	246,810	270,085	283,995	294,510	1,315,750

A brief justification of this budget is as follows:

Personnel. Timed matings, blood drawing and collection of other specimens, behavioral observations, and development and application of in vitro fertilization and embryo transfer procedures will be performed at the Medical Lake Breeding Colony. This will require a skilled veterinary technician and animal technician to assist the chief veterinarian, Dr. Blakley. A laboratory technician (50%) is required to perform routine serological and bacteria analyses, and to assist in cell culture work. A professional embryological scientist is required to develop and validate the in vitro fertilization and culture products. Student helpers provide inexpensive assistance for night and weekend work, and behavioral observations.

A research associate (100%) is needed to oversee the Infant Laboratory work and schedule and coordinate all activities on the project. This will be a professional scientist in a behavioral research area, skilled in statistical analysis and computer programming. The Infant Laboratory work will require laboratory technicians to (i) conduct learning tests, (ii) take quantitative observations on home cage and playroom social behavior, and (iii) conduct measurements of growth and reflexes. These positions will not start until grant month 18. Student helpers are needed in the Infant Laboratory for weekend and night infant care and to assist in behavioral data collection.

A full time research technician is required to perform analyses of bloods for endocrine assays. Part time laboratory technicians are needed to perform analyses of chromosomes and to analyze fetal and placental materials.

In addition to these personnel, the Principle Investigator and a number of collaborating investigators will provide 5-50% of their time with no salary paid by the project. The Infant laboratory also provides personnel for labor-delivery duty, routine care of infants, veterinary services and routine health and growth assessment. The Primate Center provides secretarial, necropsy, and pathology services, as well as animal technician and janitorial help. These form a major portion of the per diem charges. The Primate Center and the Child Development Center also provide electronic services for repair and maintenance of equipment, apparatus construction, computer analysis, and video taping. Media services for photography and drafting are also available. Equipment. Apparatus needed for a cell culture laboratory will have to be purchased as these and related items are not currently available at Medical Lake. Additional TV equipment for monitoring pregnant females will be needed, as well as items for behavioral tests. To accomodate the animals on this project along with other ongoing projects, additional time mating cages and

cages for housing pregnant females will be needed. A floppy disk for entering data at high speeds into the Primate Center Prime Computer will be needed once data are generated at the Infant Laboratory. Items will be needed for repair and replacement of worn equipment throughout the study. It should be noted that upwards of \$500,000 in computer and other equipment vital to the conduct of this work are already available and operating.

Supplies. Glassware, paper, test tubes, syringes, data sheets, medicines, chemicals, magnetic tape, and infant formula will be needed at one or more of the laboratories participating in this work.

Animal Acquisition & Per Diem. The Primate Center charges set fees when a project uses or produces an animal for experimental studies. A portion of these fees are returned as a credit toward new animals when a monkey is returned to stock in a usable condition. A standard per diem fee pays for services outlined above, portions of building heat and maintenance costs, animal feed, medicines, and other items.

Contracted Services. A number of laboratories will provide special services to this project. The Department of Neuropathology will perform light and electron microscopic examinations of brains; Dr. Kalter at the Southwest Foundation in San Antonio, Texas, will analyze specimens for evidence of simian viral infections; and blood typing will be performed by Dr. Socha of the LEMSIP laboratories in New York State. The University of Washington Academic Computer Services will be used for analyses of large data sets.

Travel. Medical Lake is 250 miles from Seattle, across the Cascade Mountains. Personnel must make regular trips to discuss the project. This is done by a \$75/round trip flight. Travel will increase in alternant years as more trips will be required to coordinate activities and discuss progress.



## SCIENTISTS AVAILABLE TO THIS PROJECT

A number of scientists in Seattle and other parts of the United States are interested in collaborating on this project or maintaining an active consulting role. By role and areas of expertise related to this project, some of these include:

Principle Investigator: Gene Sackett, Professor, Psychology; Behavioral and Physiological Development

Co-Principle Investigator: Gerald Blakley, Supervising Veterinarian, Primate Center Breeding Colony; Reproductive Biology and Primate Husbandry

Co-Principle Investigator: Harvey Schiller, Associate Professor Obstetrics; Reproductive Biology and Endocrinology

### Collaborators

Richard Blandau, Professor Biological Structure; Reproductive Biology  
Roger Donahue; Fertilization and Ova Culture

William Morton, Supervisory Veterinarian, Primate Center; Reproductive Biology  
Ellis Giddens, Assistant Professor Pathology, Primate Center Pathologist; Anatomy and morphological abnormalities in primates

Thomas Shepard, Professor Pediatrics; human and primate Embryology, Teratology, Cytogenetics

Ervin Emanuel, Professor, Epidemiology & Pediatrics; Epidemiology of poor pregnancy outcomes

Laura Newell-Morris, Professor of Anthropology; Physical growth of fetal and infant monkeys

Richard Holm, Chief, Data Management Facility, Child Development & Mental Retardation Center; Behavioral Development, Computers, and Statistical Analysis of longitudinal Experiments

Ellsworth Alvord, Jr.; Professor Neuropathology; Abnormal brain development

S. Mark Sumi; Associate Professor Neuropathology; Electron Microscopic study of brain abnormalities

Donald Farrel; Associate Professor Neuropathology; Neurochemistry

Wladislaw Socha; Professor Pathology; New York University; Immunological mechanisms in nonhuman primates

Gerald Ruppenthal; Supervisor, Infant Primate Research Laboratory; Primate infant care and development

John Glomset; Professor, Medicine & Biochemistry; Human and primate genetics, atherosclerosis, molecular structure of lipoproteins

Consultants

James Kraemer; Professor Veterinary Medicine; Texas A&M; in vitro fertilization and embryo transfer in primates

Richard Dukelow; Professor Endocrinology; Michigan State University; Primate Reproductive Biology

Alan Hodson; Professor Neonatology; University of Washington; Development of the human and primate fetus

Robert Guthrie; Assistant Professor, Neonatal Biology; Respiration of the human and primate newborn

Thomas Clarkson; Professor Medicine; Bowman-Gray School of Medicine; Primate reproductive biology, genetic and dietary aspects of cholesterol metabolism

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IN VITRO FERTILIZATION IN PERSPECTIVE, RELATIVE TO THE  
SCIENCE AND ART OF DOMESTIC ANIMAL REPRODUCTION

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## I. INTRODUCTION

This is a draft report at present, written without time for external coordination or revision. It is prepared from the standpoint of the science and art of reproduction of domestic animals, whereby man has interposed self into a tiny segment of the reproductive process for the purpose of livestock improvement. The ethical and moral questions obviously are different from those in the area of human procreation. The latter have been considered by experts, the press and lay population. For those of us concerned for both human and animal welfare, but dealing scientifically with animal aspects, it is much easier to deal objectively with the animal. This I will attempt to do. My concern for humans, however, is evident from a series of seminars I was asked to give at Cornell and elsewhere in 1975, called "Embryo Culture and Transfer: Techniques and Application in Animals and Implications for Humans."

## II. SELECTED REPRODUCTIVE CHARACTERISTICS OF SEVERAL DOMESTIC ANIMALS

Dr. Biggers has provided an excellent comprehensive review of the work with humans and laboratory animals. There is a large body of data accumulated in domestic animals which ordinarily does not reach our various library abstracting and literature search services. This has been true in artificial insemination, freezing of spermatozoa and now in vitro handling of eggs and embryos, followed by transfer to recipients. While it is more difficult to run controlled experiments with many replicates in large animals, the work with the cow is particularly relevant. A cow is a cow, but there are several characteristics which are more similar to humans than are found in our common laboratory animals (mice, rats and rabbits, for example). Several reproductive characteristics of

the cow are as follows:

1. Normally bears only one young.
2. Incidence of twinning is 2-4% depending on breed, age, parity and nutrition.
3. Superovulation leads to crowding and embryo mortality.
4. Embryo is in the 8- to 16-cell stage when it reaches the uterus.
5. Gestation length is about 280 days.
6. Reproductive life is about 15 to 20 years.

Another asset is their economic value. Although experimental animals are costly, many commercial organizations can provide low cost material as a part of their commercial operations. Examples would be artificial breeding and embryo transfer organizations in cattle.

The horse also bears single young normally in the body of the uterus, has a long gestation length of about 340 days and a reproductive life span of 30 years (Foote, 1975a). The goat bears 1 to 3 young following a gestation length of about 150 days with a maximum reproductive life of 15 years. The ewe is similar, excepting a breed of Finnish sheep that has litters. The other major farm animal, the pig, usually is maintained commercially for a short time. Their high reproductive rate of about 10 pigs per litter following a gestation of 113 days permits rapid turnover. Maximum reproductive life is estimated to be 10 years (Foote, 1975a).

Techniques for collecting semen, semen preservation, insemination, embryo collection and transfer are available in all these species (Betteridge, 1977a; Foote and Onuma, 1970; Gordon, 1975; Rinfret and Petricianni, 1978; Rowson,



1976; Salisbury, VanDemark and Lodge, 1978; Seidel, 1978). However, in vitro fertilization work is limited.

### III. IN VITRO FERTILIZATION AS A COMPONENT OF THE PROCESS OF REPRODUCTION.

Understanding fertilization is extremely important. One of the objectives of in vitro fertilization studies is to learn more about this process. However, by itself it is of little physiological significance. In order for the in vitro fertilization itself to be successful the following links in the chain of events all are important.

1. Fertile spermatozoa must be available.
2. Viable oocytes must be obtainable.
3. Proper environment for fertilization must be provided.
4. A suitable host is needed - healthy recipient at the right stage of the reproductive cycle.
5. Effective transfer technique must be used. \*
6. Young should be evaluated for normality.

#### A. Source of Spermatozoa.

The need for fertile spermatozoa is obvious. To have the spermatozoa available at the propitious moment to carry out in vitro fertilization may require holding or storing sperm cells for a period of time. The effects of storage in the liquid and frozen state recently have been reviewed (Foote, 1975b, Pickett and Berndtson, 1974; Rinfret and Petricciani, 1978; Salisbury, VanDemark and Lodge, 1978). With proper storage continuously at  $-195^{\circ}\text{C}$ , spermatozoa can be utilized for several years without any detectable decrease in fertility and with no reported increase in congenital defects. Typical results are summarized in Table 1 (Foote, 1978a). There are no significant changes with age of semen stored at  $-195^{\circ}\text{C}$ .

TABLE 1. Fertility of Bull Semen Stored For up to Several Years at -195°C.

Method of storage	Length of time stored	Number of inseminations	Fertility, % <sup>b/</sup>	
			Actual	Diff. from control
Ampules <sup>a</sup>	0.5 years	1,460	71.0	-1.1
	1.0 "	1,253	72.6	+0.5
	1.5 "	1,197	69.6	-2.5
	2.0 "	1,084	73.4	+1.3
Straws <sup>a</sup>	0-1	2,035	68.9	+1.3
	1-2	2,016	67.2	+1.7
	2-3	1,917	66.7	+2.0
	5	2,035	67.5	+2.9

<sup>a/</sup> Ampules and straws were different studies and should only be compared internally.

<sup>b/</sup> Fertility was based on cows not requiring reinsemination within 2-3 months of first insemination.

In the study with straws freshly frozen semen from the same bulls was used and the bulls' fertility may have declined with time (increasing age). Other studies with bull spermatozoa frozen in pellets gave similar results (Pickett and Berndtson, 1974) in contrast to semen stored under variable field conditions (Salisbury and Lodge, 1978).

With the application of artificial insemination to cattle in the 1940's there was concern about the normality of the offspring. Various surveys of calves born revealed no increase in defective progeny (Foote, 1978b). With frozen semen the possibility of a similar problem arose. The first use of frozen semen was accompanied by lower fertility. The National Association of Animal Breeders took special precautions to monitor progeny born. Again, fortunately there were no complications detected among the progeny. As far

as can be established poor freezing techniques kill more spermatozoa and lower fertility, but do not produce defective progeny. As freezing techniques improved, so did the initial conception rate. Thus, the sperm cell's machinery necessary for its own survival seems to be more susceptible to damage than the hereditary material contributed to its progeny.

There have been more than 100,000,000 cattle inseminated artificially with liquid and frozen semen in the U.S. No congenital problems ascribable to this process have been reported. Several generations of cattle have been produced as a result. There are several technicians who have inseminated more than 100,000 cows. Because of the intensive programs of testing and selecting sires, productive traits have improved markedly and undesirable recessive genes have been selected against.

Information is more limited in other species, including humans. However, the available evidence (see Sherman in Rinfret and Petricianni, 1978) supports the conclusion that cryopreservation of spermatozoa preserves genetic integrity of human spermatozoa.

#### B. Source of Oocytes.

Dr. Biggers (1978) has pointed out several problems associated with obtaining oocytes either directly from the ovary, or following ovulation or induced super-ovulation. The most natural condition is to obtain one oocyte or egg after ovulation in monotocous species such as the cow and the human. However, the yield per attempt is low, so in cattle the number of ovulations has been increased by superovulation. The treatment is similar to that used to induce ovulation in certain infertility cases in humans associated with anovulation. The response is variable (Gordon, 1974; Foote and Onuma, 1970). A question immediately raised is "Are superovulated oocytes normal, particularly as additional follicles which may be starting to undergo atresia appear to be rescued?"

(Moor and Trounson, 1977). We attempted to answer that in rabbits by a direct comparison of normally ovulated and superovulated oocytes (Maurer, Hunt, Van Vleck and Foote, 1968). Following transfer of 538 fertilized eggs, 60.1% of those obtained by superovulation and 54.6% obtained following normal ovulation, developed into normal young ( $P > .05$ ). In another experiment more than 3000 embryos were transferred (Maurer and Foote, 1971) to study a variety of factors affecting embryo survival and normality of young. Again fertilization rate and successful transfer rate were high and young were normal.

Age of the donor had a marked effect on the survival of embryos if left in the donor. Embryos from young and old donors both survived poorly when transferred to old recipients (sub-optimal uterine environment), but the reverse transfer of embryos from young and old donors to young recipients resulted in good survival following transfer. A composite summary from several reports (Larson et al., 1972, 1973; Spilman et al., 1972) is provided in Table 2.

TABLE 2. Ovulation Rate, Fertilization and Embryo Survival in in Young and Aged Does.

Expt. no.	Doe age, months		No. of ovulations <sup>a/</sup>		Eggs cleaved, %	
	Young	Aging	Young	Aging	Young	Aging
I	5	5	55	62	83	88
	6	18	54	37	88	91
	6	30	45	21	82	82
II	9	53	58	12	83	81
						12-day implants
III	9	53	-	-	5.7	0.8

<sup>a/</sup> No. of ovulations following superovulation.



It can be seen from Table 2 that ovulation rate, but not fertilization rate, declined with age of the doe. The ability of the doe to maintain viable fetuses by Day 12 of pregnancy was greatly reduced.

To what extent age of the oocyte donor affects the quality of the oocyte in species with a long reproductive life is not well known (Blandau, 1975). In cattle, oocytes are stored for up to 20 years (Fig. 1, Erickson, 1966a, b) without any known effects on progeny. Total reproductive failure occurs while

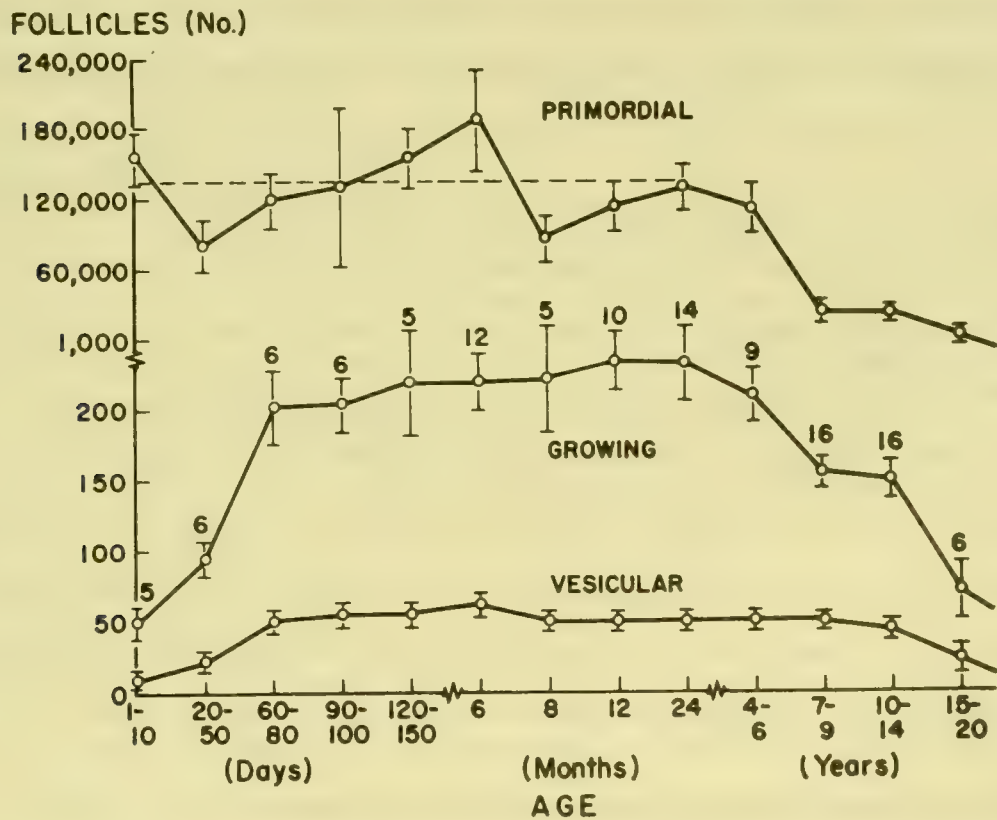


Fig. 1. Quantitative estimation of the number of primordial, growing and vesicular follicles in the postnatal bovine ovary. Vertical bars represent standard errors and numbers are the ovarian pairs examined. From Erickson (1966b).

there are still oocytes remaining (Erickson, Reynolds, and Murphree, 1976). Only a few of the oocytes ever reach the tertiary follicle stage and are ovulated. Old cows have been successful donors of oocytes in cattle embryo studies.

In humans, oocytes also are produced in large numbers during fetal development (Biggers, 1978). Down's syndrome is associated with aging ovaries, as a result of failure of the meiotic apparatus. So far as can be determined with animals, the manipulation in vitro does not add additional genetic complications for the oocyte beyond the natural process.

These results previously mentioned, as well as others from cattle, sheep, and swine (Foote, 1971; Seidel, Larson, Spilman, Hahn and Foote, 1971) reveal that exposure of the fertilized egg to a hostile environment in utero causes embryo mortality. The harvest of ovarian oocytes could overcome this difficulty. Surgical procedures are available to harvest ovarian oocytes. However, such oocytes have not been exposed to natural selection which results in considerable early embryonic loss (Biggers, 1978; Newcomb, Rowson and Trounson, 1976). Thus a substantial number die in vivo, and in vitro treatment would not be expected to salvage these. Research is needed to determine methods of identifying those which would be destined to die a natural death or provide an in vitro environment which would duplicate the natural selection process. Such an embryo culture environment might be an extension of the one provided for in vitro fertilization.

#### C. Pre-fertilization Changes in Spermatozoa in the Female.

In most species carefully studied, spermatozoa deposited in the female tract are not able to penetrate the investments of the egg immediately. A period of capacitation is required. Capacitation and the associated acrosome reaction undergone by spermatozoa is the subject of extensive reviews (Chang, 1975; Brackett, 1978b). In the pig, capacitation is believed to require about 3 hours

(Hunter and Dziuk, 1968); in sheep only about 1.5 hours is required (Mattner, 1963). In the cow the time may be 3 to 4 hours (Iritani and Niwa, 1977), but this is difficult to establish in animals with highly variable ovulation times (Mahajan and Menge, 1966). In vitro fertilization would appear to be the ideal arrangement to test capacitation in terms of the delay in sperm penetration time (Brackett and Oliphant, 1975). But if conditions are not proper, capacitation may not occur. The corollary is simple. If capacitation is required and does not occur normally then in vitro fertilization will not occur normally. Successful capacitation of sperm cells while the oocyte is still viable becomes obligatory for successful in vitro fertilization.

#### D. In Vitro Fertilization Per Se.

Success with in vitro fertilization has been limited outside of a few laboratory species (Seidel, Kane and Bowen, 1976; Bigger, 1978; Brackett, 1978a, b), and in the small laboratory animals fertilization rates are variable. Lack of capacitation may have been a factor in some experiments. Boar sperm required capacitation in order to penetrate the zonaless hamster ovum (Imai, Niwa and Iritani, 1977).

1. Evaluation in culture. A variety of criteria have been used to assess in vitro fertilization (Biggers, 1978), but proof requires evidence of participation of the male genome. If the conceptus is a male this would be proof, but this usually cannot be ascertained until a many-celled embryo is present. About half of the conceptuses (XX) could not be distinguished without male genetic markers. If spermatozoa have penetrated the egg, induced the cortical granule reaction and fused with the female pronucleus, fertilization is considered by most to have occurred. This is no assurance, however, that full development will ensue.

Menezo, Gerard and Thibault (1976) obtained 495 oocytes from Graafian follicles 2-5 mm in diameter and cultured them for 30 hours in a defined medium. The oocytes underwent the maturation division but spermatozoa did not apparently capacitate and penetrate the oocyte.

Twenty-five cow eggs were recovered from the oviduct or ovary by Brackett, Oh, Evans and Donawick (1978). Of these 56% were fertilized by spermatozoa "capacitated" with hypertonic treatment, as evidenced by loss of the cortical granules. Four of seven eggs cultured for 38 hours developed into the 4-cell stage. Frozen spermatozoa were ineffective in a single trial (Brackett, 1978b). Limited success (Von Bregella, Gerlach and Hahn, 1974) was obtained by incubating follicular oocytes in a medium supplemented with calf serum. Frozen-thawed spermatozoa were washed and incubated with cervical and uterine secretions, or were incubated in the uterus in vivo. Limited cleavage was achieved in culture following "in vitro fertilization."

Follicular bovine oocytes were cultured for 20 to 24 hours (Iritani and Niwa, 1977) until the second metaphase was reached. Spermatozoa were pre-incubated and placed with the oocytes with results given in Table 3. Fertilization occurred only in the presence of reproductive tissue add to basic buffer (KRB)

TABLE 3. Fertilization In Vitro of Cattle Oocytes Matured in Culture.

Incubation of spermatozoa	Number of oocytes	% of oocytes to Met. II.	% of oocytes fertilized
12-14 h in KRB	62	61	0
3-4 hr. cow oviduct	48	60	21
3-4 hr. sow uterus	44	61	18
3-4 hr. doe uterus	78	60	21

Iritani & Niwa, J. Reprod. Fert. 50:119-121. 1977.



2. Evaluation by in vitro/in vivo techniques. Several researchers have transferred oocytes to a recipient to be fertilized in vivo. In one study Hunter, Lawson and Rowson (1972) recovered oocytes from cow ovaries at slaughter. After brief incubation the oocytes were placed into the oviducts of recipients in estrus which had been inseminated. Of 55 oocytes transferred 29 were recovered. Sixteen of these had been penetrated by sperm and 11 were in the pronuclear stage. Another study demonstrated the importance of stimulating the oocytes. Oocytes were obtained from follicles following gonadotrophin treatment. Previous studies had shown that the oocytes with an expanded cumulus mass were in metaphase II, whereas those with a compact cumulus mass were only in the germinal vesicle stage. Oocytes and bull sperm were transferred to the oviducts of cattle or swine. None of the 26 unstimulated oocytes were fertilized, but 11 of the 31 transferred stimulated oocytes were fertilized as judged by pronuclear formation and extrusion of polar bodies.

In another study (Shea, Latour, Bedirian and Baker, 1976) 450 bovine follicular oocytes were incubated for up to 36 hours in Ham's F-10 medium with 10% fetal calf serum. In media at pH 7.0 to 7.3, 69% of the oocytes matured to metaphase II. Immature pigs and cycling ewes were selected as recipients because of the low cost (Bedirian, Shea and Baker, 1975; Shea et al., 1976). Oocytes cultured for 28 hours were transferred along with bull spermatozoa to the infundibulum of the oviducts and recovered 15 to 30 hours later. Results are in Table 4.

TABLE 4. Penetration of Cattle Oocytes by Bull Sperm in Sheep and Pig Oviducts Following In Vitro Culture of Oocytes for 28 hours.

Bovine oocytes cultured	<u>Type of recipient</u>	
	Sheep	Pig
Oocytes transferred, no.	24	67
Oocytes recovered, %	67	43
Oocytes with a polar body, %	88	69
Oocytes with spermatozoa, %	50	55
Oocytes penetrated, %	0	17

Shea et al., J. Anim. Sci. 43:809. 1976.

Note that in the pig oviducts, at least, bull spermatozoa were able to be capacitated and fertilize the oocytes. The authors noted that many of the oocytes likely came from atretic follicles and that a system which would identify those oocytes with potential for development would be desirable.

Finally, Shea (1978) has established pregnancies following transfer of follicular oocytes (Table 5). The proportion of successful results is low,

TABLE 5. Fertilization of Bovine Follicular Oocytes in Recipients.

Variable	Result
Follicles aspirated, no.	1219
Oocytes obtained, %	64%
Oocytes transferred, no.	182
Recovery 5 days later, %	49%
Fertilized ova recovered, %	32%
Transferred to recipients, no.	10
Pregnant, no.	4

Shea. Theriogenology 9:101. 1978.

and demonstrates the need for sufficient material to carry out stepwise research. Application of these techniques to 7 infertile valuable cows yielded 10 embryos which produced 5 pregnancies upon transfer to recipients.

Early work in sheep (Dauzier and Thibault, 1959) resulted in 4 out of 78 eggs with polar body formation when sperm cells previously recovered from ewes were added to eggs in vitro. When fresh sperm were added to 41 eggs there was no evidence of fertilization. These data are interpreted to reveal a need for using capacitated spermatozoa. More recently Cran et al. (1976) and Moore and Trounson (1977) have obtained normal young following transfer of matured oocytes to recipients in which the oocytes were fertilized and developed

into young. In the studies by Moor and Trounson (1977) the first results with culture of oocytes were discouraging, in that culture in media such as TC199A resulted in initiation of meiosis but not in normal development following transfer of oocytes to oviducts and spermatozoa to uteri of recipient ewes. Earlier work with rabbits had revealed that culture of oocytes within the follicle would lead to normal maturation in vitro.

Subsequently, follicles were cultured. Supplementation of the TC199A medium with 1  $\mu\text{g/ml}$  of estradiol 17- $\beta$ , 2  $\mu\text{g/ml}$  of FSH and 1  $\mu\text{g/ml}$  of LH greatly increased the number of blastocysts which developed. In one experiment 391 follicles 2 to 5 mm in diameter were recovered from PMSG-injected ewes. After culture for 24 hours oocytes were transferred to the oviduct of ewes in estrus which had been inseminated. Seven days later 96 oocytes or embryos, which had been cultured in this medium, were recovered and 37 were blastocysts with >100 cells. Further experiments gave the following results when oocyte source was classified according to the type of follicles:

	<u>Blastocysts</u>
Oocytes from small nonatretic follicles	26%
" " large "	46%
" " atretic follicles	50%

Finally, 34 blastocysts and 4 morulae obtained were selected at random and transferred to suitable recipient ewes, along with 42 control blastocysts recovered from ewes mated 7-9 days previously. Results were as follows:

1. Experimental embryos produced 24 lambs = 63%
2. Control embryos produced 22 lambs = 52%

Work with pigs has progressed slowly (Hunter and Polge, 1966; Harms and Smidt, 1970; Herrman and Holtz, 1977; Iritani, Niwa and Imai, 1978). The

earlier work revealed limited oocyte maturation in culture, but without normal fertilization. The need for using capacitated spermatozoa was suggested. Recently Iritani et al. (1978) cultured pig follicular oocytes obtained from follicles 2-5 mm in diameter. They were incubated for 4.5-5 hours at 37° C with sperm in a synthetic medium plus bovine serum albumin, with and without oviducts or uteri from recently slaughtered sows. The oocytes with pronuclear formation were 1/17 (6%) in buffer, 9/28 (32%) with oviduct present and 14/36 (39%) with uterine tissue present. Similar results were obtained when ejaculated instead of epididymal spermatozoa were used.

Considerable attention is now being given to the pig for basic work on fertilization (Dunbar, Wardrip and Hedrick, 1978; McGanghey, 1977; Tsafriri, Pomerantz and Channing, 1976), partly because of the high yield of material at low cost. With several of the technical problems partially overcome by improvements in culture media and sperm preparations, this species may provide a useful model for screening ideas and techniques.

It is clear that simple activation of the oocyte when spermatozoa are added to the medium is not sufficient evidence for in vitro fertilization. The only very satisfactory technique to assess the efficiency and the risk is through embryo transfer and the production of young. This can be done most simply by transferring embryos to recipient animals at the same stage of the estrous cycle. These are not always available, but synchronization between embryo and recipient could be achieved if the embryo could be stored. Therefore a brief account of the present status of embryo freezing is included.

3. Storage of embryos by freezing. Embryos can be stored at ambient temperatures above freezing for several hours in normal culture media without



loss of viability (Seidel, 1977). This permits direct transfers to be made between donors and recipients with short intermediate culturing. However, when it is necessary to transport embryos over considerable distances (Shea, Ollis and Jacobson, 1977), or store embryos until a suitable recipient is available, then longer storage by freezing has considerable potential. Successful technology in this field would permit banking of unique germ plasm, preservation of endangered species, selective livestock breeding, and storage of embryos to increase animals of commercial importance, such as by twinning in cattle (Anderson, 1978).

There are reviews on the freezing of mammalian embryos (Ciba Foundation Symposium 52 edited by K. Elliott and J. Whelan, 1977; Maurer, 1978). Also appended to this report is a list of references on embryo freezing. The species most studied is the mouse (Whittingham, 1977). Various media, "seeding" temperatures, freezing rates and thawing rates have been tested to give maximum survival. It is not within the scope of this report to more than call attention to the rapid progress made in this field during the past few years.

The principles found to be important for preserving mouse embryos have been useful in preserving embryos of other species. However, species differences exist. The 8-cell mouse embryo has been preserved most successfully. In cattle, sheep and goats morulae and blastocysts have been frozen successfully. A brief summary of experiments with domestic animals in which frozen-thawed embryos were transferred to foster mothers and allowed to develop into young is summarized in Table 6. This is taken from the literature (see Maurer, 1978). Results are variable. At the present time it appears that about 30% of the embryos frozen, thawed and transferred will develop into young. This is about half the effective

TABLE 6. Frozen Embryo Transfer Studies in Cattle and Sheep Summarized from the Literature.

Species	Cryo-protectant	Number frozen	Progeny (%)
Sheep	1.5 M DMSO	62	13
"	"	34	32
Cattle	2.0 M DMSO	33	3
"	1.5 M DMSO	15	7
"	"	61	15
"	"	39	31
"	"	10	60
"	1.0 M glycerol	9	44

Maurer. Theriogenology 9:59. 1978.

rate of 60% expected when embryos are transferred to recipients without being exposed to the freeze-thaw process.

Embryos can be stored for a long time at  $-195^{\circ}\text{C}$ , but do not survive at normal household freezer temperatures. This is similar to the experience with sperm cells. Mouse embryos stored for 369 days were cultured and transferred following freezing and thawing (Maurer, Bank and Stamples, 1977). Freezing did cause some cellular damage, as fewer embryos survived than was true for unfrozen controls. Young born were normal, and grew and reproduced at the same rate as controls. The progeny of the frozen embryo parents also were normal. Thus, again the results appear to be an all or none phenomenon. Those that survive appear to have an unaltered development and presumably a "normal" genotype. For further details the references appended should be consulted.

#### E. Embryo Transfer - The Embryo, the Recipient and the Result.

Throughout the discussion it is evident that the final evaluation of any in vitro handling of the gametes or embryos requires transfer to suitable

recipients so that young born can be determined and examined. This has been the standard scientific test against which other criteria are measured.

The technology has become sufficiently advanced that thousands of progeny have been produced, primarily in cattle in the past five years. These have been produced in selective breeding programs, to cope with possible disease problems and to overcome certain types of infertility (for example, tubal blockage), to mention a few examples. Much can be learned from these commercial operations because of their scope and because they had to carry on extensive and expensive research and development programs. Consequently, they offer factual evidence of the effectiveness and risk of the process when carried out by experts under practical conditions. Again, there are excellent recent compilations of the state of the science and art (Betteridge, 1977; Rowson, 1976; and E. E. C. Conference at Galway, Ireland on "Control of Reproduction in the Cow," to be published soon).

Surgical techniques were required to recover and transfer most of the embryos until recently (Elsden and Betteridge, 1977; Foote and Onuma, 1970; Murray, 1978; Onuma, Hahn and Foote, 1970). Many factors affected the efficiency of the process besides the skill of the operators (Church and Shea, 1977; DuMesnil du Buisson, Renard and Levasseur, 1977). These included (1) health of the donor and recipient, (2) superovulatory response (Gordon, 1975; Elsdén, Nelson and Seidel, 1978), (3) fertility of the spermatozoa used, (4) stage of the embryo recovered, and (5) synchrony between the donor and recipient. Donor and recipient should be in estrus within one day of each other for best results (Rowson, Moor and Lawson, 1969).

Culture media and conditions of holding embryos between collection and transfer are important, but many procedures have been used successfully when

embryos are stored for only a few hours (Seidel, 1977). Modified TC199A Ham's F-10 and similar media are used.

Stage of development and "quality" of the embryo are factors also. A large series of bovine embryos (Shea et al., 1976) was classified according to their appearance, compactness, symmetry and density of blastomeres. Results are in Table 7. The subjective evaluation was partially effective in predicting

TABLE 7. Pregnancies Following Transfer of Embryos Judged to Differ in Quality.

Stage of embryo	Classification	Transfer results	
		Number	% pregnant
Morula	Excellent	59	64
	Good	409	61
	Average	1709	56
	Fair	350	44
	Poor	14	29
8-12 cell	Excellent	1	0
	Good	28	43
	Average	330	43
	Fair	281	36
	Poor	44	18

Shea et al. C.E.C. 145. 1976.

success. The 8-12 cell stage embryos did not develop as well, perhaps because some were retarded or they had undergone less natural selection. In another study over 500 embryos were transferred (Elsden, Nelson and Seidel, 1978). The pregnancy rates resulting from transferred embryos classified as poor, fair, good or excellent were 12, 31, 58 and 63%, respectively.

There is an advantage of transferring the embryo to the same side that has the corpus luteum when only one embryo is transferred (Del Campo et al., 1977).



Transferral of two embryos increases the chances of a cow becoming pregnant (Anderson, 1978).

Selected cases of infertility have been overcome by embryo transfer (Bowen, Elsdon and Seidel, 1978). These include occlusions of the oviducts.

Nonsurgical embryo collection and transfer is used widely in cattle at the present time (Brand and Drost, 1977a, b; Elsdon, Hasler and Seidel, 1976; Sreenan, 1978; Trounson, Rowson and Willadsen, 1978). This is less expensive and frequently is used to aspirate single embryos from donors on the farm to be transferred to recipients on the same farm. In these cases usually no selection is practised, unless the embryo clearly is not viable. The technique is about 75 to 80% as efficient as the surgical technique in recovering embryos and in transferring them. The success depends greatly upon the skill and experience of the operator. Some have improved their efficiency from about 50% of the results by surgical methods to becoming nearly as efficient.

The progeny from embryo transfer appear to be normal (Betteridge, 1977; Seidel, personal communication, 1978). No organization or research group has reported anomalies so far as I am aware. However, there is a need for a systematic follow-up and examination of progeny born in comparison with a control group with the same sires and dams producing calves without transfer of embryos.

Many types of research have been conducted (Gordon, 1977). Of particular interest is the possibility of correctly sexing the embryo without damaging it. At the present time the bovine embryo can be sexed by removing cells from the trophoblast, but many embryos are damaged in the process (Hare and Betteridge, 1978). (Sex selected spermatozoa are offered in the human field currently, although the effectiveness of the process remains to be established).

Other species. Less information is available in other species. Non-surgical techniques appear to be quite successful in horses (Oguri and Tsutsumi, 1974; Allen, 1977). Progeny have been produced by embryo transfer in sheep and goats (Betteridge and Moore, 1977; Lawson, 1977; Moore, 1977). Surprisingly little work has been done with the pig (Betteridge, 1977; Dziuk and Day, 1977; Polge, 1977). Perhaps it is because the economic benefits are limited in a species as prolific as swine. The requirements for culturing eggs are similar to other species (Davis and Day, 1978).

The general principles which provide the foundation for successful egg collection and transfer in one species apply to other species. Therefore, should similar techniques be useful under special circumstances in human medicine, there is a basis for belief that the knowledge gained with these species would assist greatly in establishing optimal procedures for humans.

## CONCLUSIONS

Fertilization in the natural environment is still not well understood. The actual combining of the spermatozoon and oocyte is only a small part of the total process of procreation in mammals. In vitro fertilization offers a scientific tool to understand bits of this process. Application of the technology of which in vitro fertilization is a part to selected problems, such as blocked oviducts, has resulted in successful treatment in cattle and a much publicized limited result in humans.

Research and development of technology in domestic animals, particularly cattle, has much to offer in the way of facts and experience. Cattle, for example, provide an opportunity to study single conceptuses over a long

period of gestation. Research, as adjuncts to commercial (clinical) programs, can result in extensive studies that otherwise would be economically prohibitive.

Research with domestic animals, along with laboratory animals, has provided greater insight into (1) the kinds of follicular oocytes which have the greatest potential in culture; (2) sperm prefertilization requirements; (3) more nearly optimal culture systems for fertilization and early development; (4) possibilities for karyotyping and selecting the more viable embryos for transfer; (5) the need to carefully synchronize donor and recipient. The normality of young born in domestic animals gives some assurance that the techniques do not produce defective progeny. Yet, this is but one of the many gaps that require further investigation.

Only when we have knowledge can there be intelligent application. Without sufficient knowledge there will be inept application to meet the needs. Throughout history the best in veterinary and human medicine has resulted from a mixture of application and fundamental research.

In times of demand to meet a need, where the technology is not fully developed, we need more good science, not less. This means carefully planned, well conducted research which is clearly reported when results warrant publication. This is the kind of research NIH supports.

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HOW DOES ONE ASSESS THE RISK OF ABNORMALITIES FROM  
HUMAN IN VITRO FERTILIZATION?

James J. Schlesselman, Ph.D.



## INTRODUCTION

The procedure of in vitro fertilization, including the collection of mature ova, the use of embryo culture, and the subsequent transfer of a human preimplantation embryo into the uterus of the oocyte's donor, gives rise to concern about risks of the technique. Biggers (1978a) suggested four ways in which the incidence of abnormalities might be increased: (i) induction of chromosome aberrations, (ii) increased rate of fertilization by abnormal spermatozoa, (iii) induction of point mutations, and (iv) effect of physical and chemical teratogens on malformations.

Rather than focus on the mechanisms by which an abnormality might be induced, I shall concentrate on outcomes which can be observed and which provide a basis for assessing a potential alteration in risk. Briefly stated, the question is whether "the techniques used for in vitro fertilization, culture and transfer increase the incidence of abnormality above that existing naturally" (Biggers, 1978a). The apparent simplicity of this question is rivalled only by the complexity that shall arise in providing an answer. The nub of the problem derives from the phrase "existing naturally". The golden rule that the results of all in vitro studies should be evaluated in terms of the normal events in the intact organism (Biggers, 1978a) imposes the task of establishing a reference or standard for comparison. The first point in this regard is that the reference group of women, whose pregnancies establish the rates of abnormalities expected in vivo, should be similar to the in vitro group

in respect to all major characteristics which are known to affect the frequency of chromosome anomalies and spontaneous abortion. With this requirement satisfied, any differences between the groups in the frequency of abnormalities is more likely due to some aspect of the in vitro procedure. A second consideration based upon the principle of comparing "like with like" relates to the embryos themselves. The frequency of anomalies should be compared in embryos or fetuses of the same developmental age and deriving from the same pregnancy outcome.

An example of the preceding considerations is easily given. The study by Hook (1978) indicates that bias would invalidate a comparison of the frequency of trisomy among blastocysts deriving from in vitro fertilization with that detected in vivo by amniocenteses done at 16 weeks gestation. Blastocysts with trisomy may either fail to implant, or implant but abort before an amniocentesis is performed. Since abnormal embryos are more likely to be eliminated in the early stages of pregnancy, one expects a higher rate of trisomies among blastocysts as compared to the rate observed among fetuses at the time of amniocentesis. (I assume that the amniocenteses are not done on women who were referred because of a chromosome abnormality in a previous pregnancy.)

Stages of embryonic development at which an abnormality is detected may occur either pre- or post-implantation. Taking first the preimplantation phase, in vitro experiments can provide data on the frequency with which human ova fail to be fertilized, or are fertilized by one or more spermatozoa. Preimplantation blastocysts can also be karyotyped to determine the frequency of chromosome anomalies among them. Subsequent to implantation, there are three sources of information relating to abnormalities: (i) spontaneous



abortions, (ii) amniocenteses, and (iii) live births and fetal deaths. Concerning spontaneous abortions, both the rate of embryo loss and the prevalence of chromosome anomalies among the abortuses will be pertinent. Amniocentesis can provide data on the prevalence of chromosome anomalies, enzyme deficiency diseases, and congenital malformations (anencephaly and spina bifida). Live births and fetal deaths can provide data on chromosome abnormalities and congenital malformations.

Table 1 outlines an approach to studying the risk of abnormalities, and provides a guide to the discussion in the next section. The answer to the question "how frequently do chromosome abnormalities occur in vivo among preimplantation blastocysts?" will be shown to depend partly upon postimplantation findings. Thus, beginning with an overview of intrauterine mortality from fertilization to birth, the next section continues with a review of postimplantation data from in vivo studies, and then proceeds to preimplantation results.

## POSTIMPLANTATION

### A. Spontaneous Abortions

#### 1. Frequency of Embryo Loss

Table 2 is based upon Leridon's (1977) complete table of intrauterine mortality, using the findings of Hertig (1967) for the first two weeks after ovulation, and the data of French and Bierman (1962) for the remainder of the follow-up periods. Hertig estimated that under conditions optimal for fertilization "about 15 percent of oocytes fail to become fertilized, about 10 to 15 percent segment but fail to implant, about 70 to 75 percent (at least 58 percent) implant but only 42 percent are of such viability as to cause the patient to miss her expected menstrual period." One can see from

Table 2 that Leridon assumed that 16 ova per 100 failed to be fertilized. Of the 84 ova which are fertilized, 15 failed to implant, thus resulting in 69 implantations per 100 ova exposed to optimal in vivo conditions. As Hertig (1967) himself has stated "The probable curve of fertility prior to day 25 is conjectural, based on the 8 segmenting ova (4 normal and 4 abnormal) from the tube and uterus and the 5 early implanted ova of 7 and 9 days of age. It is supposed that the ultimate curve would resemble that of any domestic animal which ovulates but one oocyte at a time." Thus the embryo loss up to the second week after ovulation, at which time an estimated 42 embryos are still viable, is based upon human data from only 13 embryos.

A brief digression is useful at this point to explain some terminology which recurs throughout the remaining discussion. The gestational age of a fetus is traditionally determined from the first day of the last menstrual period (LMP) prior to pregnancy (implantation). The developmental age of an embryo or fetus is determined from the day of fertilization of the ovum, approximately the 14th day in a 28 day menstrual cycle. Thus the reference point from which gestational age is determined occurs about two weeks prior to the reference point for developmental age. In some instances data are reported in terms of weeks post-implantation. Since implantation occurs approximately 6 days after fertilization, a fetus of 4 weeks gestation is 1 week postimplantation; a fetus of 2 weeks development is also 1 week post-implantation. In reading the biomedical literature, one must keep these distinctions in mind, because investigators have generally reported the age of embryos in terms of developmental age, the age of fetuses in terms of gestational age, and the age of abortuses in terms of either developmental or gestational age.

Computation of the rates of embryo loss, spontaneous abortions, live births, and so on, requires careful attention to the use of different reference points. Consider the data in Table 2, which shows 31 live births resulting from 100 ova exposed to spermatozoa under ideal in vivo conditions. Taking the 100 ova as the reference point, a loss of 69% [ $= (100 - 31)/100$ ] has occurred. If one considers fertilization as the reference, the loss is 63% [ $= (84 - 31)/84$ ], whereas the loss is only 55% [ $= (69 - 31)/69$ ] in terms of implantations. In terms of the 42 embryos viable at two weeks after ovulation, the loss is 26% [ $= (42 - 31)/42$ ]. This last figure is comparable to the rate given by French and Bierman (1962), who estimated that for every 1,000 pregnancies viable at 4 - 7 weeks gestation, 237 result in a spontaneous abortion or a fetal death.

Alberman and Creasy (1977) give a convenient summary of additional terminology:

"The expulsion from the uterus of a conceptus before it is potentially sufficiently mature to survive is described as a spontaneous abortion, miscarriage, or early fetal death. In the United Kingdom viability is conventionally assumed to be attained by the 28th week after the first day of the mother's last menstrual period, though in many other countries 22 or 24 weeks is considered a more realistic time. The delivery of a dead fetus after this stage of pregnancy is known as a stillbirth or late fetal death. The death of a stillborn fetus may have occurred before or during the delivery. Intra-partum death generally results in the delivery of a fresh fetus ('fresh stillbirth'), while fetuses which die ante-partum show varying degrees of maceration ('macerated stillbirth'). The death of an infant within a week of birth is an early neonatal death, and stillbirth and early neonatal death combined are termed perinatal death."

Table 3 gives estimates of the frequency of spontaneous abortions (and fetal deaths) per 1,000 pregnancies. The data derive from French and Bierman's (1962) careful study of mortality based upon a follow-up of 3,083 pregnancies occurring on the island of Kauai during the four year period

1953-1956. Kauai lies 100 miles northwest of Honolulu. At the time of study, the island had a population of about 30,000 people. The women whose pregnancies were followed were predominantly of Japanese (38%), Filipino (21%), or Hawaiian (17%) origin. Their median age at the time of the first pregnancy studied was 26 years. Medical conditions on the island were "as favorable as or better than [those] for the rest of the United States for life expectancy at birth, proportion of women receiving prenatal care, and proportion of infants born in hospitals." Kauai had a birth rate similar to that of the U.S. white population and its infant mortality rate was 10% lower than that for U.S. whites. French and Bierman's study was designed to provide information about early pregnancies based upon reports from women as soon as they suspected they were pregnant. There were 592 pregnancies identified between 4-7 weeks gestational age. Table 3 shows that for every 1,000 viable pregnancies recognized between 4 and 7 weeks gestation 237 aborted spontaneously or terminated as a fetal death.

Table 4 is taken from Leridon (1977), who recalculated the data of French and Bierman to allow for very early spontaneous abortions that were undoubtedly missed. Leridon also calculated the intrauterine mortality deriving from five other studies. The columns headed by  $q_x$  represent the conditional probability of a spontaneous abortion occurring in the following 4 weeks, given that the pregnancy is viable at the start of the interval. To take an example, the first column headed  $q_x$  shows that 10.8% ( $= .108 \times 100\%$ ) of pregnancies viable at the beginning of the 4th week will abort at some time during the interval 4 through 7 weeks. Among pregnancies viable at the beginning of the 16th week, 1.3% ( $= .013 \times 100\%$ ) will abort at some time during the interval 16 through 19 weeks.



The columns in Table 4 headed by  $d_x$  represent the number of spontaneous abortions that will occur in each month, assuming that one starts with a fixed cohort of 1,000 pregnancies, and that this cohort is depleted through the occurrence of spontaneous abortions and fetal deaths. Thus, taking the first column labeled " $d_x$ " and starting with 1,000 pregnancies, 108 abort during the interval 4-7 weeks, leaving 892 viable at the start of the 8th week. Of these 892 pregnancies, 62 ( $= 892 \times 0.070$ ) abort during the interval 8-11 weeks. Thus 830 pregnancies remain at the start of the 12th week. Of these, 37 ( $= 830 \times 0.045$ ) abort during the interval 12-15 weeks, and so on.

The last two rows in Table 4 give the total number of spontaneous abortions and fetal deaths that would be expected to occur at some time between 4-27 weeks (or 4-39 weeks) in a cohort of 1,000 pregnancies viable at the start of 4 weeks gestation. The estimates of a spontaneous abortion occurring at some time during 4-27 weeks gestation range from a low of 123 per 1,000 pregnancies to a high of 312 per 1,000 pregnancies. In absolute terms, the estimates of  $q_x$  are moderately consistent across studies, although on a percentage basis the variation is considerable.

## 2. Chromosome Abnormalities in Spontaneous Abortions

### a. Variation by Developmental Age

The frequency of chromosome abnormalities in spontaneous abortions has been reported to vary from 8 to 64 percent<sup>†</sup> (Carr and Gedeon, 1977). A large part of this variation is due to studies being based upon abortuses of different developmental ages. Figure 1 (Boué and Boué, 1976) derives from a study (Boué and Boué, 1974) of human spontaneous abortions in which the developmental age of a specimen was determined from a morphologic examination of the embryo and a detailed histologic examination of the placenta. Among the 1,097 abortuses between 2 to 7 weeks of age, 724 (66%) had an abnormal karyotype. The frequency of anomalies fell to 23% among the 108 abortuses between 8-12 weeks of age. The study of Creasy, Crolla and Alberman (1976)

reported 287 chromosome anomalies among 983 karyotyped abortuses, giving an overall frequency of 29%. Since this rate is based upon all unselected spontaneous abortions up to 27 weeks gestation, it is not directly comparable to that reported by the Boués. Alberman and Creasy (1977) reviewed studies by Carr (1967), Dhadial et al (1970) Creasy et al (1976), Therkelsen et al (1973), Arakaki and Waxman (1970), Kujii et al (1973) and Boué et al (1975). They estimated that the frequency of chromosome abnormalities in spontaneous abortions decreased "from over 60% in the earliest detectable stages of pregnancy to below 5% by the end of the sixth month."

#### b. Variation by Maternal Age.

Approximately 21% of recognized pregnancies in young women (less than 20 yrs) end in a spontaneous abortion or fetal death. The rate is lowest (16%) among women 20-24 years old, and rises steadily with increasing maternal age, so that among women over forty years of age, approximately 50% of recognized pregnancies fail to produce a live birth. The frequency of chromosome anomalies in spontaneous abortions is lowest among the youngest women, and increases with advancing maternal age. Table 5, based upon estimates of Leridon (1977, Table 4.19), indicates that chromosome anomalies appear in 59% of spontaneous abortions in women 20-24 years of age. Among women 35-39 years old, 74% of spontaneous abortions have a chromosome abnormality.

The frequency of spontaneous abortions (including fetal deaths) given in Table 5 refers to that occurring in recognized pregnancies. The overall rate, taken from French and Bierman's (1962) estimate of 237 losses per 1,000 pregnancies, was adjusted by the age-specific rates given by Shapiro et al (1962). The percentage of chromosome abnormalities in spontaneous abortions was based upon the results of the Boués (Leridon and Boué, 1971). Since the

Boués derived their estimates predominantly from spontaneous abortions of 14 weeks gestation or less, the figures for the percentage of anomalies given in Table 5 are probably too high. The important point of this table is the indication that the frequency of chromosome abnormalities expected in spontaneous abortions depends upon maternal age..

c. Relative Frequency of Various Types of Chromosome Abnormality

Carr and Gedeon (1977) summarized the relative frequencies of various types of chromosome abnormalities which were found in eight different studies of spontaneous abortions. Table 6, which was taken from their report, shows that approximately 52% of the chromosome abnormalities were due to trisomy. The relative frequency of trisomy varied from a low of 42% (based on 76 abortions with chromosome abnormalities) to a high of 57% (based on 215 abortions with chromosome abnormalities). The relative frequency of triploidy, which represented about 18% of the chromosome abnormalities, varied among the studies from 10% to 22.5%. Translocations, although not shown in Table 6, accounted overall for 3.2% of chromosome abnormalities, varying from a low of 1.3% to a high of 4.2% (Carr and Gedeon, 1977, Table 4).

d. Frequency of Translocation Abnormalities Among Parents  
Who Conceived Embryos Which Were Spontaneously Aborted

Kajii and Ferrier (1978) conducted a prospective cytogenetic survey of couples with a history of recurrent abortions. The parents of 430 abortuses were karyotyped, in 353 cases both parents, and in 77 cases one parent. Table 7 shows the frequencies of translocations in parents who conceived embryos which were aborted and in the general population of parents. The rate of structural chromosome abnormalities among the aborters (0.8 percent) was significantly higher than that found in the general population (0.3 percent).

The rates of translocation carriers were higher among the aborters with a history of recurrent abortions (2.7 percent) and among aborters with a history of perinatal deaths (3.6 percent) than among those without such histories (0.6 percent). Due to the small number of translocation carriers, neither one of these two differences was statistically significant. *This study again emphasizes that the rates of specific chromosome abnormalities cannot be assumed to be constant for all couples within a specified population.*

#### B. Amniocentesis

First performed and described by Schatz (1882) as a possible treatment for polyhydramnios, diagnostic amniocentesis performed at approximately 16 weeks gestation can now detect all recognized chromosome abnormalities, more than 60 inborn errors of metabolism, and indicate congenital malformations arising from open neural-tube defects, including anencephaly and spina bifida (NICHD Amniocentesis Study Group, 1976; Milunsky, 1976). The procedure involves inserting a needle through the abdomen and into the uterus in order to withdraw a sample of amniotic fluid which contains fetal cells. Amniocentesis has been done primarily on restricted groups of women who are at high risk of bearing an abnormal child, advanced maternal age (35 years or older) being the most common reason for prenatal genetic studies. The next accepted indication for amniocentesis has been the occurrence of a chromosomal translocation in either parent (Milunsky, 1976).

##### 1. Chromosome Abnormalities

The rates of chromosomal anomalies reported from prenatal diagnosis has been tabulated by Milunsky and Atkins (1977), who presented the results in Table 8 based upon twelve references occurring in the period 1972 to 1975. The frequency of abnormalities detected by amniocentesis increases with



advancing maternal age; 2.2 percent of women aged 35-39 have an abnormal fetus versus 3.4 percent for women 40 years of age or older. Milunsky and Atkins (1977) state that the 3.4 percent rate of abnormalities in the over 40 age group is likely to appreciably underestimate the risks in women over 44 years of age.

The rate of chromosome abnormalities among fetuses of women referred for amniocentesis solely because of advanced maternal age would serve as an appropriate age-specific comparison for amniocenteses in women having in vitro fertilization. The data presently available in this respect are unlikely to be very helpful, however, since the findings relate to women 35 years of age or older, whereas one would expect that most women having in vitro fertilization would be younger than 35. Of course younger women have had amniocentesis performed. Since they have generally been referred because of either a previous pregnancy with a chromosome abnormality or a family history of cytogenetic disorders, they represent a group at high risk for chromosome abnormalities, and consequently would not provide an appropriate comparison. Park Gerald (1978) has suggested that a way to avoid this bias would be to establish a rate of chromosome abnormalities in younger women who were referred for amniocentesis because of either a previous pregnancy with an inborn error of metabolism or a neural-tube defect (anencephaly and spina bifida). Neither one of these conditions is believed to affect the risk of a chromosome abnormality in a subsequent pregnancy. The NICHD Amniocentesis Study Group (1976) reported that 90 women were referred for amniocentesis because of a previous birth with a metabolic disorder. None of these women had a chromosome abnormality detected at amniocentesis (Bryla, 1978). Milunsky and Atkins (1977) provide data which indicates that of 100 women referred for amniocentesis because of either a previous neural tube defect (55) or a metabolic disorder (45), three had a

fetus with a chromosome abnormality. The proportions of abnormalities from these two sources are not significantly different ( $p = 0.28$ , two-sided Fisher's exact test). The combined data give a rate of chromosome abnormalities of 1.6% (3/190), with lower and upper 90% confidence limits of 0.1% and 3.1% respectively.

The study by Hook (1978) emphasizes the importance of using the same sources of diagnoses in any comparison of the rates of abnormalities. Hook reported a survey of pregnancies in which a chromosome anomaly was diagnosed by amniocentesis, but in which some mothers declined an elective abortion. For 19 singleton fetuses with Down's syndrome, the spontaneous fetal death rate after amniocentesis was 21 percent, significantly higher than the rate of 2.7 percent among 73 fetuses with less seriously abnormal genotypes. Thus a major fraction of the discrepancy observed between the maternal-age specific rates of Down's syndrome in live births and the rates found at amniocentesis is undoubtedly due to spontaneous fetal loss.

## 2. Enzyme Deficiency Diseases

The frequency of inherited metabolic disorders detected by amniocentesis has generally been reported only for women at high risk of bearing a child with this condition. These rates provide an appropriate comparison only for similar high risk women having an in vitro fertilization. One may consult Milunsky and Atkins (1977) and the report of the NICHD amniocentesis registry (Lowe et al, 1978) for further details.

## 3. Neural-Tube Defects

The comments of the preceding section apply to the use of the assay for elevated levels of alpha-fetoprotein to determine the frequency of anencephaly and spina bifida at amniocentesis.

### C. Live Births and Fetal Deaths

Live births and fetal deaths represent the next point at which one might consider looking for a possible increased risk of abnormalities. One expects, however, that pregnancies resulting from in vitro fertilization would be monitored with sufficient care to prevent the occurrence of chromosome abnormalities at birth. This would involve karyotyping fetal cells using amniocentesis at about 16 weeks gestation. It is at this stage, rather than at birth, that the preventive measure of elective abortion is available.

#### 1. Chromosome Abnormalities Among Live Births

Hook and Hamerton (1977) summarized six series of newborn chromosomal investigations that had been published as of June 1976. Table 9 gives the rates of autosomal and sex chromosome abnormalities per 1,000 live births. These rates are presented separately for males and females within each center, and are also combined across centers. Since the study by Walzer and Gerald (1975, 1977) was done only on male live births, the combined rate of abnormalities for males and females excludes their results. As an overall summary, approximately 6.2 chromosome abnormalities

(4.0 autosomal and 2.2 sex chromosome) can be expected per 1,000 births. The variation in the rates of abnormalities which were reported by the six studies is of some interest. For example, considering total chromosome abnormalities among male live births, the rates vary from a low of 4.0 per 1,000 to a high of 9.2 per 1,000. The rates among females vary from 3.9 per 1,000 to 7.4 per 1,000. In either case, one encounters roughly a two-fold variation in the reported rates.

Patil et al (1977) report the frequency of chromosome abnormalities ascertained in a survey of 4,342 children between the ages of seven and eight

years. Although not directly comparable to the results obtained from live births, a rate of 4.8 abnormalities (2.5 autosomal and 2.3 sex chromosome) per 1,000 children was reported.

## 2. Congenital Malformations

Abnormalities arising from a single mutant gene are referred to as Mendelian disorders (Erbe, 1976). The DNA which comprises a gene may develop an error in replication (mutation) and result in abnormal protein synthesis. This may manifest itself as an inborn error of metabolism, or cause multiple anomalies or an isolated malformation. The most common inherited enzyme deficiency thus far identified in humans is glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. The gene for this X-linked disorder is so prevalent among blacks in the United States that 12 percent of the males have G-6-PD deficiency, 24 percent of females are carriers, and about one in 140 black females has homozygous G-6-PD deficiency (Erbe, 1976).

The Meckel syndrome is an autosomal recessive disorder due to a single mutant gene (Holmes, 1976). The multiple anomalies which characterize this syndrome include occipital encephalocele, cleft lip and palate, microphthalmia, polycystic kidneys, genital anomalies, equinovarus foot deformity and post-axial polydactyly. Although isolated anomalies due to Mendelian inheritance may occur in any organ system, malformations of the limbs are the best known (Holmes, 1974). By 1975 there were 2,336 Mendelian phenotypes which had been described (McKusick, 1975). They are generally quite rare, most occurring at rates of 1 per 100,000 to 1 per million births. In restricted populations, the frequency of conditions such as Tay-Sach's disease or sickle cell anemia may be as high as 1 per 100 to 1 per 10,000 (Benirschke et al, 1976).



There is no universal agreement on what constitutes a congenital malformation. "In most studies a working definition of congenital malformations is established which, in the last analysis, depends upon the opinion and judgment of the investigator(s)." The Collaborative Perinatal Project of the National Institute of Neurological Disease and Stroke defined a congenital malformation as a "gross physical or anatomic developmental anomaly which was present at birth or was detected during the first year of life." The diagnoses were based on criteria and instructions given in manuals which were written by panels of experts to assure uniform diagnostic practices at the twelve institutions participating in the study throughout the United States (Myrianthopoulos and Chung, 1974).

Malformations are commonly classified as being either major or minor. Generally speaking, a major malformation is a condition which has surgical or cosmetic consequences (Holmes, 1976). Major malformations include cleft lip and palate, congenital heart disease, pyloric stenosis, congenital dislocation of the hip, and spina bifida and anencephaly. These conditions are thought to arise from the combination of the effects of two or more deleterious genes (Erbe, 1976 ; Benirschke et al, 1976). Approximately one infant in every 200 (0.5 percent) has a malformation that is attributed to the combined effects of environmental factors and two or more deleterious genes (multifactorial inheritance). The rates of specific major malformations are given in Table 10. As one might expect, the mode of ascertainment is most important, and these rates are approximations of uncertain precision. Centrally collected government statistics yield rates which are lower than those based upon examinations by teams of specialists interested in congenital malformations (Sholtz et al, 1976). Rates based only upon live

births would also be expected to differ from those based upon data which includes fetal deaths, since the rates of malformations among the latter group are higher.

Table 11 shows the variation encountered in the reported incidence of selected major malformations. The method of ascertainment differs among the nine studies which are summarized, and this undoubtedly accounts for a large part of the variation in the rates. Kennedy (1967) reviewed the world literature on the incidence of congenital malformations, and his extensive tabulation of results, along with several additions found between 1965 and 1975, can be found in the review by Sholtz et al (1976).

The Collaborative Perinatal Project, representing the largest investigation of pregnancy and pregnancy outcomes reported to date, enrolled about 56,000 pregnant women for study during the first months of their pregnancy. The women were followed through labor and delivery, and their children were followed to the seventh year of life. This study found that only a little more than one-third of all congenital malformations are recognized at birth (Myrianthopoulos and Chung, 1974). Table 12 reports the rates of malformations which were found at birth and during the first year of life among single births in 24,153 whites and 25,126 blacks. These rates, reported per 10,000 births, include malformations in 1,004 fetal deaths and 877 neonatal deaths. Of the 37 major malformations listed in Table 12, fifteen show significant differences between the rates for whites and blacks.

Table 13 shows separately for whites and blacks the percentages of major and minor malformations among males and females. Approximately 8.5% of births (including fetal and neonatal deaths) had a major malformation. Males in general are more frequently malformed than females. This is entirely

due to an increase in the rate of major malformations among males (Myriathopoulos and Chung, 1974). In addition to differences by race and sex, considerable variability in the rates of major and minor malformations occurred among the 12 institutions participating in the Collaborative Perinatal Project, despite the use of a standard protocol. For births with only a major malformation, the frequency varied from a low of 4.0% to a high of 9.3%. The frequency of births having only a minor malformation varied from 4.5% to 14.5% (Myrianthopoulos and Chung, 1974, Table 10).

#### PREIMPLANTATION

##### A. Fertilized Ova

###### 1. Polyspermy

The use of microscopy to determine the frequency of polyspermy among preimplantation ova fertilized in vitro would yield information for which no adequate in vivo comparison is now available. Biggers (1978b) reports that the totality of in vivo information relating to human preimplantation ova and embryos is confined to 15 specimens, nine recovered from the oviduct and six from the uterus. Regarding human ova and embryo loss during the first two weeks after exposure to spermatozoa under ideal in vivo conditions, Leridon's (1977) table of intrauterine mortality (see Table 2) is based on Hertig's (1967) conjectures which derive from an examination of the morphology of only 13 human ova.

Soupart and Strong (1974) used electron microscopy to detect 2 abnormal fertilizations out of 16 human ova exposed to spermatozoa in vitro. Of the 2 abnormal zygotes, one resulted from two spermatozoa penetrating a single ovum. Biggers (1978a) has noted that the proportion of abnormal fertilizations ( $2/16 = 0.125$ ) observed by Soupart and Strong

(1974) approximates Hertig's (1967) estimate that 10 to 15 percent segment but fail to implant. In respect to concern with an increased risk of polyspermy, or the fertilization of ova by abnormal spermatozoa, the comparison is not completely satisfactory. Biggers (1978a) points out that the 14 ova penetrated by a single sperm are not guaranteed normal development, because either the sperm or the ovum may have an abnormal chromosome complement as a result of non-disjunction during meiosis. Another problem with the comparison is that it does not specifically address the issue of polyspermy, and it appears that no in vivo data is available to make an adequate comparison at such an early stage of embryonic development.

In discussing their findings of 26 triploid fetuses among 340 spontaneous abortions, Jacobs et al (1978) estimate that 66% of triploids were the result of dispermy; 24% resulted from fertilization of a haploid ovum by a diploid sperm, and 10% were the result of a diploid ovum being fertilized by a haploid sperm. Of course this data does not provide a proper comparison for the rates of triploidy among preimplantation ova fertilized in vitro. Moreover, the estimate by Jacobs et al (1978) that 1-3% of all recognized conceptions result in triploidy would also not apply to the preimplantation phase.

## B. Blastocysts

### 1. Chromosome Abnormalities

The problems of comparison raised in respect to polyspermy in preimplantation ova also apply to any chromosome anomalies detected by karyotyping blastocysts. Since the preponderance of in vivo data derives from spontaneous abortions occurring in recognized pregnancies, the most reliable in vitro comparisons of abnormalities will result from pregnancies of



duration longer than two weeks postimplantation.

Approximately 40% to 50% of implantation blastocysts can be expected to have a chromosome abnormality in vivo. This estimate is derived in the following manner. An implanted blastocyst can result in a spontaneous abortion, a stillbirth (fetal death), or a live birth. For these three outcomes, Table 14 gives the frequency of chromosome abnormalities at various intervals subsequent to implantation. Data on chromosome abnormalities from Boué and Boué (1976), reported in weeks of development, and from Creasy, Crolla, and Alberman (1976) and Alberman and Creasy (1977), reported in weeks of gestation, have been abstracted and converted in Table 14 to weeks postimplantation. Using this data and Leridon's (1977) estimates (see Table 2) of intrauterine mortality, Table 15 gives the numbers of chromosome abnormalities, per 1,000 implantations, which would occur during various intervals.

The last column of Table 15 shows that for every 1,000 implanted blastocysts, approximately 457 have a chromosome abnormality. This estimate depends partly upon my assumption that at 0 weeks postimplantation 95% of spontaneous abortions have a chromosome abnormality (see Tables 14 and 15). Alternatively, if one assumes that at 0 weeks postimplantation 78% of spontaneous abortions have a chromosome abnormality, one derives a conservative figure of 396 abnormalities per 1,000 implantations. Assuming that 100% of spontaneous abortions have a chromosome abnormality at 0 weeks postimplantation, one calculates that 477 abnormalities per 1,000 implantations will occur. Thus an estimate of 40% to 50% seems plausible for the in vivo frequency of chromosome abnormalities among implanted blastocysts. Allowing for the fact that some blastocysts undoubtedly

fail to implant because of anomalies, the expected frequency of chromosome abnormalities among preimplantation blastocysts would be higher than the preceding estimates.

Boué, Boué and Lazar (1975) estimated that about "1 out of every 2 conceptions has a chromosome anomaly." Although such a figure may be appropriate for a population as a whole, Boué and Boué (1976) emphasize that the risk of conceiving abnormal embryos is extremely variable among couples. This latter point may be illustrated indirectly by a study (Boué et al, 1973) based upon follow-up, from 6 months to 4 years, on 774 women who had an initial abortion which was karyotyped. As shown in Table 16, the risk of another abortion in these women depended on maternal age, the existence of a chromosomal anomaly in the previous abortion, and the reproductive history prior to the initial abortion which was karyotyped. Some of the rates in Table 16 are based upon very small samples, and as a consequence, they are not precise.

#### HOW LARGE A SAMPLE DOES ONE NEED?

##### A. Operating Characteristic

##### 1. Power of the Chi-Square Test for a Difference Between an Observed Rate and an "Expected" Rate

Let us put aside for the moment the problem of establishing a rate for any particular abnormality occurring in vivo, against which the rate deriving from in vitro fertilization may be compared, and consider next the issue of how large a series of in vitro fertilizations and implantations would be required to reliably detect a potential increase in the rate of a specific abnormality. In comparing the in vivo and in vitro rates, one might err in either of two ways: Type I error - claiming that a difference exists, when in fact it does not; Type II error - claiming that no difference

exists, when in fact there is a difference.

The probability of making a Type I error is called the level of significance, and is commonly denoted by the symbol " $\alpha$ ". The probability of making a Type II error is represented by the symbol " $\beta$ ". The quantity  $1 - \beta$ , called the power of a statistical test, represents the probability of detecting a difference in the rates, when a difference truly exists. Since either a Type I or a Type II error is undesirable, one wants both  $\alpha$  and  $\beta$  to be small. Equivalently, one desires that  $\alpha$  be small and  $1 - \beta$  be large.

Suppose that a specific abnormality occurs in vivo at a rate of  $r_1$ (%) and that the unknown rate in vitro is  $r_2$ (%). Assume that, in respect to risk factors which affect the rates of abnormalities, women whose pregnancies derive from in vitro fertilization are otherwise comparable to women whose pregnancies occur in vivo. Then it is intuitively clear that the larger the sample of embryos, the better is one's chance of detecting a true difference  $\delta = r_2 - r_1$  in the rates of abnormalities. It is also clear that large differences are more easily detected than small ones.

The rate of abnormalities in a sample of  $n$  embryos deriving from in vitro fertilization can be regarded as an estimate of the unknown value of  $r_2$ . Sampling fluctuations will cause the value of the estimate  $\hat{r}_2$  to vary around  $r_2$ , so that the observed difference  $\hat{r}_2 - r_1$  may be much less than the true difference  $\delta = r_2 - r_1$ . The power (probability of detecting a true difference  $\delta$ ) becomes larger with increasing sample size, and the operating characteristic or power curve quantifies the relationship between the power  $1 - \beta$ , the sample size  $n$ , and the difference in rates  $\delta$ . Given an estimate or expected value for  $r_1$ , and specifying  $\alpha$  to be small (say  $\alpha = 0.05$ ), the

operating characteristic is a graph of the power  $1 - \beta$  as a function of the sample size  $n$  for various hypothetical values of  $\delta$ .

## 2. Sample Size for Studies of Chromosome Abnormalities in Blastocysts

Figure 2 provides a specific example of an operating characteristic. Assuming that the in vivo rate of chromosome abnormalities among implantation blastocysts is equal to  $r_1 = 50\%$  (Boué, Boué and Larzar, 1975), the four power curves give the probability of detecting a hypothetical increased rate of abnormalities for in vitro studies of various sizes. For instance, suppose that one had in vitro data from  $n = 20$  blastocysts. If the rate of abnormalities in vitro were truly equal to  $r_2 = 60\%$ , then a sample of  $n = 20$  blastocysts would give only a 13% chance ( $1 - \beta = 0.13$ ) of finding that  $\hat{r}_2$  was significantly ( $\alpha = 0.05$  two-sided) greater than  $r_1$ . A sample of  $n = 50$  blastocysts would give one a 30% chance ( $1 - \beta = 0.30$ ) of detecting the increase, and a sample of  $n = 200$  would give one an 80% chance of detecting the increased risk. If the rate of abnormalities in vitro were truly equal to  $r_2 = 80\%$ , however, one would need a sample of only  $n = 50$  blastocysts to virtually guarantee ( $1 - \beta = 0.98$ ) that the increased rate would be detected. From an inspection of Figure 2, one can begin to appreciate that there is no single answer to the question of how large a sample one needs.

As an alternative to thinking in terms of a difference in rates,  $\delta = r_2 - r_1$ , one may wish to consider their ratio  $R = r_2/r_1$ , which is called the relative risk. Values of  $R$  greater than 1.0 indicate that the rate of abnormalities arising in vitro exceeds that arising in vivo.

At lower right in Figure 2, the values of the relative risk  $R$  have been given corresponding to each of the values of  $r_2$  used for the four power curves. The value  $R = 1.2$  ( $60/50$ ) represents a 20% increase in



risk over the expected rate of  $r_1 = 50\%$ . The value  $R = 1.4$  ( $70/50$ ) represents a 40% increase in risk over the expected rate, and so on.

### 3. Assumptions Underlying the Sample Size Analysis

Appendix A provides a more complete discussion of the operating characteristic, and gives the formulae from which the power curves in Figures 2-6 were calculated.\* The article by Freiman et al (1978), which describes the application of the operating characteristic to the design of randomized clinical trials, provides another elementary discussion.

The power curves in Figures 2-6 derive from a sample size formula (Appendix A, equation (3)) which is based upon several assumptions. The first is that the "in vivo" rate of abnormalities  $r_1$  is specified without considerations of error. Thus if one agrees, for example, with the assessment of Jacobs et al (1978) that spontaneous abortions deriving from recognized conceptions have a rate of triploidy between one and three percent in vivo, then a value for  $r_1$  should be specified between 1% and 3%. Taking  $r_1 = 3\%$  would be conservative in the sense that an observed rate of  $\hat{r}_2 = 3\%$  deriving from in vitro fertilizations would not differ from that "expected in vivo". On the other hand, given a sufficiently large sample,  $\hat{r}_2 = 3\%$  would result in a highly significant chi-square test against  $r_1 = 1\%$ . Thus the result of any significance test should be tempered by an appreciation for the precision (or lack thereof) with which an "expected" rate can be specified.

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\*The derivations and formulae in Appendix A are given in terms of proportions, whereas the present discussion is in terms of rates (percentages, frequency per 100).

A second assumption is that the rate  $r_1$  applies uniformly to all in vitro fertilizations. The analysis in Appendix A does not distinguish the results of 25 in vitro fertilizations attempted for one woman from the results of a single attempt in 25 women. Given the dearth of information on individual variation, and the fact that the rates of abnormalities reported "in vivo" derive from numerous women, one can only state that the rate  $r_1$  should be regarded as an average across women, and that analyses of data deriving from studies of in vitro fertilization should distinguish the number of women from the number of fertilizations, implantations, spontaneous abortions, etc.

A third assumption, of less importance than the previous two, is the approximation of the binomial distribution by the normal distribution. Feller (1968, pp. 182-190) gives a detailed elementary discussion of this topic. Where the power  $1 - \beta$  is less than 0.05, the calculated values may have a moderate amount of error, on a percentage basis, due to the normal approximation. Since we are not especially interested in such low values of power, this point is of secondary concern. In any event, the error resulting from the numerical approximation is likely to be far less than the error deriving from the use of an estimate for  $r_1$ .

The value of the sample size  $n$  given by formula (3) in Appendix A is 1/4 as large as that applicable to the comparison of two proportions  $\hat{p}_1$  and  $\hat{p}_2$ , both estimated from samples of equal size  $N$ . In the latter case, each sample would be of size  $N = 2n$  (see Armitage 1971, p. 186), resulting in a total sample of size  $N + N = 4n$ . Considerable savings thus result from the assumption that  $r_1$  is known "without error". The savings are partly illusory, because one can never be certain that the group of women upon which

the expected rate of abnormalities occurring "in vivo" is calculated is comparable, in all major respects, to the group of women who conceive through in vitro fertilization and embryo transfer. The absence of a direct experimental control in studies of abnormalities which may arise from in vitro fertilization is a limitation which is inherent in certain types of human investigation. Another example would be human studies of whether certain drugs or chemicals are carcinogenic in man. In both situations a direct experimental approach which randomizes subjects to either a treatment or a control group would be unethical and infeasible.

#### 4. Sample Size for Studies of Frequency of Chromosome Abnormalities in Early Spontaneous Abortions.

The data of Boué and Boué (1976) suggest that 66% of spontaneous abortions of 2-7 weeks developmental age (1-6 weeks postimplantation) will have a chromosome abnormality (see Figure 1). The operating characteristic shown in Figure 3 is based upon the assumption that this in vivo rate is the frequency that would be expected, if there were no adverse effect of in vitro fertilization. If, in fact, the in vitro rate were increased to 79%, then a study of  $n = 50$  spontaneous abortions occurring 1-6 weeks postimplantation would provide only a 50% chance ( $1 - \beta = 0.50$ ) of detecting the increase. Various other combinations of hypothetical increased risk and sample size may be read directly from Figure 3.

#### 5. Sample Size for Studies of the Frequency of Early Spontaneous Abortions

The data of French and Bierman (1962) indicate that for every 1,000 pregnancies viable at 4 weeks gestation, 207 ( $= 108 + 62 + 37$  from Figure 4) will spontaneously abort at some time during the interval 4 through 15 weeks gestation. Taking the rate  $r_1 = 20.7\%$  as that which would be expected in vivo,

the operating characteristic in Figure 4 shows the sample sizes required to give one high power for detecting various hypothetical increased risks. Thinking in terms of weeks postimplantation, one would be interested in detecting, among those embryos viable at 1 week postimplantation, spontaneous abortions occurring at any time during the interval 1 week through 12 weeks. For example, if the risk in vitro were increased to 31%, then a follow-up study of  $n = 50$  embryos viable at one week postimplantation would provide only a 44% chance ( $1 - \beta = 0.44$ ) of detecting the increase. A follow-up study of  $n = 100$  embryos would provide a 72% chance of detecting the increase;  $n = 170$  embryos viable at one week would be needed to give one a 90% chance.

#### 6. Sample Size for Studies of the Frequency of Major Malformations Occurring at Birth and During the First Year of Life.

Data from the Collaborative Perinatal Project (Myrianthopoulos and Chung, 1974) indicate that approximately 8.5% of births (including fetal and neonatal deaths) will have a major malformation which can be detected at birth or during the first year of life (see Table 13). The operating characteristic shown in Figure 5 uses this rate as the frequency expected among births conceived through in vitro fertilization, if there were no effect whatsoever on malformations. If the risk of a major malformation were increased to 13%, then study of  $n = 100$  births conceived through in vitro fertilization would provide only a 32% chance of detecting the increase. One would need approximately  $n = 500$  births to give a 90% chance of detecting the increased risk of  $r_2 = 13\%$ .

#### 7. Sample Size for Studies of the Frequency of Chromosome Abnormalities in Live Births.

Hook and Hamerton's (1977) summary of six studies indicates that approximately 0.62% of live births can be expected to have a chromosome



abnormality (see Table 9). The operating characteristic in Figure 6 shows that even with a hypothetical two-fold increase in risk ( $R = 2$  corresponding to  $r_2 = 1.2\%$ ), one would need a sample of  $n = 2,000$  or more births to give a high probability of detecting the increase.

## DISCUSSION

The estimate that 40% to 50% of human implanted blastocysts have a chromosome abnormality seems plausible. The rate among blastocysts prior to implantation remains conjectural, however, because we have no certain knowledge of the implantation failure rate in abnormal as compared to normal blastocysts. Given this uncertainty, Figures 2-6 indicate that the best opportunity for detecting a potential increased risk of chromosome abnormalities resides in the examination of early spontaneous abortions, particularly those occurring 1 through 6 weeks postimplantation, provided that they can be successfully identified and karyotyped. Although four times as many women have their pregnancy progress to 16 weeks gestation than have a spontaneous abortion in the preceding interval, the relatively low frequency of chromosome abnormalities expected at the time of amniocentesis suggests that early spontaneous abortions can still provide a better assessment of increased risk. The analysis is as follows.

Let  $p_1$  be the proportion of early spontaneous abortions which have a chromosome abnormality, and let  $p_1^*$  be the corresponding proportion among amniocenteses at 16 weeks gestation. Assuming that one wants to detect an increased relative risk equal to  $R$ , then the ratio of the required number amniocenteses ( $n_1$ ) to the number of spontaneous abortions ( $n_2$ ) is given by

$$n_1/n_2 = [(1 - p_1^*)p_1]/[p_1^*(1 - p_1)]$$

using equation (3) in Appendix A. For example, assuming that 1.6% of

amniocenteses will indicate a chromosome abnormality, whereas 40% of spontaneous abortions between 4-15 weeks gestation will have a chromosome abnormality, one has  $p_1^* = 0.016$ ,  $p_1 = 0.40$  and

$$\begin{aligned} n_1/n_2 &= [(0.984)(0.4)]/[(0.016)(0.6)] \\ &= 41. \end{aligned}$$

Thus one would need the results of 41 times more karyotypes at amniocentesis than at the time of early spontaneous abortion in order to detect an increased relative risk R.

The data of French and Bierman (1962) indicate that four times as many women will be available for karyotyping at amniocentesis than at the time of an early spontaneous abortion (793 vs 207, from Table 4). Given the analysis of the preceding paragraph, if each early abortion could be identified and successfully karyotyped, one would need ten times the base population for a study using amniocentesis compared to one using spontaneous abortions. If only half of the early abortions could be karyotyped, then one would need five times the base population using amniocentesis. Thus the effectiveness of early identification and the relative efficiency of successfully karyotyping spontaneous abortions alters the assessment of the total effort required.

Excluding lifelong follow-up, the "bottom line" in any current assessment of the risks of in vitro fertilization would certainly be abnormalities apparent at birth and during the first year of life. The rates of abnormalities among live births, however, are generally much lower than the rates in spontaneous abortions and fetal deaths, since prenatal elimination of abnormal embryos and malformed fetuses is the rule, rather than the exception (Roberts and Lowe, 1975). Thus the discovery of any

increased risk among live births would undoubtedly come long after evidence which strongly implicated the ultimate finding had already accumulated from spontaneous abortions. Kline et al (1977) have made the same argument in respect to using spontaneous abortions to monitor potential environmental teratogens.

The efficiency of eliminating abnormal embryos during the course of pregnancy appears to be quite high. For every 1,000 chromosome abnormalities which are present in implanted blastocysts, only 5 to 7 are expected to survive to the point of a live birth. Thus 99.3% to 99.5% of the chromosome abnormalities are eliminated in vivo through spontaneous abortion or fetal death. These estimates are derived in the following manner.

Table 2 indicates that 31 live births are expected to result from 69 implantations, so that 2,226 implantations would be needed to produce 1,000 live births. Since 40% to 50% of implanted blastocysts are expected to have a chromosome abnormality, approximately 890 to 1,113 abnormalities occur among the 2,226 implantations. Table 9 indicates that 6 chromosome abnormalities are expected among 1,000 live births. Therefore, the number of abnormalities at birth has been reduced to 6 from the original 890 to 1,113 at implantation. On a percentage basis, 99.3%(884/890) to 99.5%(1,107/1,113) of the abnormalities have been eliminated.

Provided that the medical treatment associated with in vitro fertilization does not enhance the survival of abnormal embryos, a major implication of the preceding line of reasoning is that a marked increase in the frequency of chromosome abnormalities at implantation is expected to have only a minor effect on the frequency of abnormalities among live births. Since only 0.5% to 0.7% of the abnormalities at implantation survive to the point of live

birth, a two-fold increase in the frequency of abnormalities at implantation, from 400 per 1,000 to 800 per 1,000, would result in only 2 to 3 additional abnormalities per 1,000 live births.

To take another perspective on this matter, consider the detection of a chromosome abnormality at amniocentesis as an indication for elective abortion. Suppose that 1.6% of pregnancies at 16 weeks gestation have a chromosome abnormality in vivo (see POSTIMPLANTATION, Section B,1), indicating 16 elective abortions per 1,000 amniocenteses, and that on average 31.9 fetuses of 16 weeks gestational age result from 69 implantations (see Table 2). Assuming 40% to 50% of implantations have a chromosome abnormality, one calculates that 1.5% to 1.8% of the chromosomally abnormal embryos would survive to 16 weeks gestation. Thus a two-fold increase in the frequency of abnormalities at implantation, from 400 per 1,000 to 800 per 1,000, would result in the indication of an additional 6 to 7 elective abortions per 1,000 amniocenteses.

There is the possibility that in vitro fertilization per se does not induce abnormalities, but rather that the ancillary medical treatment used to establish an implantation and maintain a pregnancy may enhance the survival of naturally occurring abnormalities. A decrease in the frequency of spontaneous abortions and the occurrence of fewer anomalies among abortuses may presage such a development. In this event, the analysis of the two previous paragraphs would need revision.

A major increase in the frequency of chromosome abnormalities at the time of implantation which is attributable to in vitro fertilization seems likely to have a comparatively minor effect on either abnormalities among live births or the indications for elective abortion at amniocentesis. On



the other hand, the induction of more abnormalities by in vitro as opposed to natural fertilization would result in more spontaneous abortions, and require more attempts at in vitro fertilization to achieve a normal live birth. Because of this, the implications of in vitro fertilization appear to be much greater for the mother than for the child, in that the mother would be repeatedly subjected to the costs and risks associated with the surgical procedure for the collection of mature ova and the hormonal treatment to induce superovulation and achieve implantation.

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## APPENDIX A

OPERATING CHARACTERISTIC FOR THE CHI-SQUARE TEST OF AN  
OBSERVED PROPORTION  $\hat{p}_2$  VERSUS AN "EXPECTED" PROPORTION  $p_1$ .

Suppose that the proportion of abnormalities occurring in vivo in a defined population of women is denoted by  $p_1$ , and that the corresponding in vitro proportion is denoted by  $p_2$ . Given our present state of knowledge, the value of  $p_2$  is unknown for any particular abnormality, and, as shown in preceding sections, values of  $p_1$  can be estimated with varying degrees of certainty, depending upon the type of abnormality of interest.

The proportion of abnormalities arising in a sample of  $n$  pregnancies deriving from in vitro fertilization may be regarded as an estimate of  $p_2$ . Denoting this estimate by  $\hat{p}_2$ , one may use the difference  $\hat{p}_2 - p_1$  to decide whether or not  $p_2$  exceeds  $p_1$ . A test of significance based upon the chi-square statistic

$$\chi^2 = n (\hat{p}_2 - p_1)^2 / [p_1 (1 - p_1)]$$

is commonly used to compare an observed proportion  $\hat{p}_2$  with an "expected" proportion  $p_1$ . Since sampling fluctuations ("chance") will cause the values of  $\hat{p}_2$  to vary around  $p_2$ , the observed difference  $\hat{p}_2 - p_1$  may be much less than the true difference

$$\delta = p_2 - p_1.$$

Large values of  $\chi^2$  are incompatible with the assumption ("null hypothesis") that  $p_1 = p_2$ . For example, if  $p_1 = p_2$ ,  $\chi^2$  will exceed the value 2.71 with probability  $\alpha = 0.10$ ;  $\chi^2$  will exceed the value 3.84 with probability  $\alpha = 0.05$ , and will exceed the value 6.63 with probability  $\alpha = 0.01$ .

Since large values of  $X^2$  are unlikely under the null hypothesis, one generally concludes that if a large value of  $X^2$  is observed, either  $p_1$  is greater than  $p_2$  (if  $p_1 > \hat{p}_2$ ) or  $p_2$  is greater than  $p_1$  (if  $\hat{p}_2 > p_1$ ).

The quantity  $\alpha$  is referred to as the level of significance of the statistical test, and it represents the probability of a Type I error. The probability of a Type II error is denoted by  $\beta$ . The quantity  $1 - \beta$  is called the power of the test, and it represents the probability that  $\hat{p}_2$  will be significantly different from  $p_1$ , if, in fact,  $\delta \neq 0$ . Since either a Type I or a Type II error is undesirable, one wants both  $\alpha$  and  $\beta$  to be small. Equivalently, one desires that  $\alpha$  be small and  $1 - \beta$  be large.

To answer the question "how large a sample should be used?", one must specify four quantities: (i) an estimate of the proportion of abnormalities expected to occur in vivo,  $p_1$ ; (ii) the minimal difference  $\delta$  which one regards as important to detect; (iii) the desired level of significance,  $\alpha$ ; and (iv) the desired power,  $1 - \beta$ . Given values for  $p_1$ ,  $\delta$ ,  $\alpha$  and  $\beta$ , the value of  $n$  is calculated from the equation

$$n = (z_\alpha + z_\beta)^2 p_1(1 - p_1) / \delta^2. \quad (3)$$

The terms  $z_\alpha$  and  $z_\beta$  are unit normal deviates corresponding to the desired Type I and Type II error rates  $\alpha$  and  $\beta$ . Table A1 gives values of  $z_\alpha$  and  $z_\beta$  for a range of values of  $\alpha$  and  $\beta$ .

Table A1

Unit Normal Deviates  $z_\alpha$  and  $z_\beta$  for Selected Values of  $\alpha$  and  $\beta$ ,  
Assuming a Two-sided Test of Significance

$\alpha(\text{or } \beta)$	$z_\alpha$	$z_\beta$
0.001	3.29	3.09
0.005	2.81	2.58
0.01	2.58	2.33
0.025	2.24	1.96
0.05	1.96	1.64
0.10	1.64	1.28
0.20	1.28	0.84
0.30	1.04	0.52

As an example of the application of equation (3), suppose that a particular abnormality occurs in vivo at the rate of 3% ( $p_1 = 0.03$ ), and that if the rate in vitro were as large as 7% ( $p_2 = 0.07$ ,  $\delta = 0.07 - 0.03 = 0.04$ ), then one would want a 90% chance ( $1 - \beta = 0.90$ ) of finding the observed difference  $\hat{p}_2 - p_1$  significant at the  $\alpha = 0.05$  level. To meet these requirements, one would need a sample of size

$$n = (1.96 + 1.28)^2 (.03)(.97)/(.04)^2 = 191$$

Equation (3) shows that for specified values of  $p_1$  and  $\delta$ , the three quantities  $n$ ,  $\alpha$  and  $\beta$  are interrelated. For a fixed sample size  $n$ , the power  $1 - \beta$  can be increased only by increasing the Type I error rate  $\alpha$ . If the size of the sample is completely at one's disposal,  $\alpha$  and  $\beta$  can be reduced to any preassigned level by using a sufficiently large  $n$ . There are other



relationships among the terms  $n$ ,  $\alpha$ ,  $\beta$ ,  $p_1$ , and  $\delta$ , the most important the being/ operating characteristic or power-curve. For specified values of  $\alpha$  and  $p_1$ , the operating characteristic is a graph of the power  $1 - \beta$  as a function of the sample size  $n$  and hypothetical values of the difference  $\delta$  (see Figures 2-6).

From equation (3) one can derive the following expression

$$z_\beta = [n\delta^2/p_1(1 - p_1)]^{1/2} - z_\alpha \quad (4)$$

Letting  $P(\cdot)$  denote the cumulative normal distribution function, the power is given by

$$1 - \beta = P(z_\beta). \quad (5)$$

A simple polynomial approximation for  $P(x)$ ,  $0 \leq x < \infty$  is given by

$$P(x) = 1 - 1/2 (1 + c_1x + c_2x^2 + c_3x^3 + c_4x^4)^{-4} + \epsilon(x) \quad (6)$$

where  $c_1 = .196854$        $c_3 = .000344$

$c_2 = .115194$        $c_4 = .019527$

The error of the approximation is bounded by  $|\epsilon(x)| < 2.5 \times 10^{-4}$

(Abramowitz and Stegun, 1964).

Table 1

Scheme for Study of Potential Increased  
Risk of Abnormalities Resulting From  
In Vitro Fertilization

PREIMPLANTATION (0-6 days)

A. Fertilized ova

1. Polyspermy

B. Blastocysts

1. Chromosome abnormalities

POSTIMPLANTATION (1 week - 38 weeks approx.)

A. Spontaneous Abortions

1. Frequency of embryo loss
2. Chromosome abnormalities in spontaneous abortions

B. Amniocentesis

1. Chromosome abnormalities
2. Enzyme deficiency diseases
3. Neural tube defects

C. Live Births and Fetal Deaths

1. Chromosome abnormalities
2. Congenital malformations

Table 2

Complete Table of Intrauterine Mortality,  
per 100 Ova Exposed to the Risk of Fertilization\*

Week after Ovulation	Deaths <sup>a</sup>	Survivors <sup>b</sup>
	16 <sup>c</sup>	100
0	15	84 <sup>d</sup>
1	27	69 <sup>e</sup>
2 <sup>f</sup>	5.0	42
6	2.9	37
10	1.7	34.1
14	0.5	32.4
18	0.3	31.9
22	0.1	31.6
26	0.1	31.5
30	0.1	31.4
34	0.1	31.3
38	0.2	31.2
Live Births. . . . .		31

\*Source: Leridon (1977, Table 4.20)

<sup>a</sup>Expulsions of dead embryos

<sup>b</sup>Pregnancies still in progress

<sup>c</sup>Not fertilized

<sup>d</sup>Number fertilized

<sup>e</sup>Number implanted

<sup>f</sup>Expected time of menses

Table 3

Estimated Frequency of Spontaneous Abortions (and Fetal Deaths)  
per 1,000 Pregnancies\*

Gestational Age (wks) <sup>a</sup>	During 4-Week Interval	From Start of Interval To End of Pregnancy
4-7	108.1	237.3
8-11	69.9	144.8
12-15	44.8	80.5
16-19	13.3	37.4
20-23	8.5	24.4
24-27	3.2	16.1
28-31	3.0	13.0
32-35	2.9	10.1
36-39	3.4	7.4
40 + <sup>b</sup>	6.8	6.8

\* Source: French & Bierman, 1962, Table 7, Columns (1) and (8).

<sup>a</sup>Gestational age determined from the first day of the last menstrual period prior to the beginning of pregnancy.

<sup>b</sup>Includes 35 live births terminating at 45-47 weeks gestation; no fetal deaths occurred after 43 weeks gestation.



Table 4

## Life Tables of Intrauterine Mortality From Various Studies\*

Duration of Gestation From LMP	French Bierman (1962)	Taylor (1970)	Petterson (1968)	Shapiro et al. (1962)	Erhardt (1963) <sup>c</sup>	Shapiro et al. (1970) (1)	(2)
x (weeks)	$q_x^a$	$q_x$	$d_x$	$q_x$	$d_x$	$q_x$	$d_x$
0					(.112) (112)		
4	.108	.061	61	.014	.082	.161	161
8	.070	.049	46	.059	.067	.135	114
12	.045	.025	23	.040	.028	.053	38
16	.013	.011	10	.014	.011	.017	12
20	.008	.008	7	.006	.009	.007	4
24	.003	.003	3	.004	.002	.004	3
28	.003	.004	3	.002	.004	.003	2
32	.003	.003	3	.003	.002	.003	2
36	.004	.004	3	.004	.007	.004	3
40	.007	.004	4	.005	.011	.002	1
44	...	.010		...		.002	
48		.018					
Deaths $\Sigma(4-27)$	225	150	125		166	312	209
Deaths $\Sigma(4-39)$	232	159	125		175	339	217

\*SOURCE: Leridon, 1977, Table 4.3

<sup>a</sup>Conditional probability of death during 4-week period ( $q_x$ ), given survival at the beginning of the period<sup>b</sup>Number of deaths during 4-week period ( $d_x$ ) for a cohort of 1,000 pregnancies followed from 4 weeks gestation<sup>c</sup>Life table adjusted and extrapolated by its author<sup>d</sup>Week 7 only

Table 5

Frequency of Spontaneous Abortions (SA) per 1,000 Pregnancies  
and Percentage of Chromosome Anomalies (CA) Among  
Spontaneous Abortions, by Maternal Age\*

	< 20	20-24	25-29	30-34	35-39	≥ 40
SA per 1,000 Pregnancies	207	162	192	261	366	500
CA per 100 Spontaneous Abortions	42	59	58	65	74	85

\*Source: Leridon, 1977, Table 4.19; spontaneous abortions include fetal deaths

Table 6

## Relative Frequencies of Types of Chromosome Abnormalities\*

Reference	Total No. of Abnormal	%Trisomy	%45,X	%Triploid	%Tetraploid	%Other
Boué, Boué & Lazar (1975)	921	52	15	20	6	7
Creasy & Alberman (1975)	287	50	24	13	4	9
Kajii (1975)	215	57	20	10	3	10
Therkelsen & Lauritsen (1975)	140	44	29	10	8	9
Takahara (1975)	94	56	13	20	2	9
Dill (1975)	76	42	9	28	14	7
Carr (1967) <sup>a</sup>	50	52	24	18	4	2
Carr and Gedeon (1977) <sup>b</sup>	<u>80</u>	<u>52.5</u>	<u>11</u>	<u>22.5</u>	<u>9</u>	<u>5</u>
Total/Mean	1,863	52	18	17	6	7

\*Source: Carr and Gedeon, 1977, Table 2

<sup>a</sup>Unselected, consecutive hospital abortions<sup>b</sup>Selected because of phenotypic abnormality

TABLE 7

Frequencies of Translocations in Aborters  
and in General Adult Population\*\*

<i>Population</i>	<i>Individuals karyotyped</i>		
	<i>Total no. karyotyped</i>	<i>Structurally abnormal</i>	
		<i>No.</i>	<i>%</i>
General adult population	9,616	30	0.3*
All aborters	783	6	0.8*
Nonrecurrent aborters	710	4	0.6
Recurrent aborters	73	2	2.7
Aborters without history of perinatal death	727	4	0.6
Aborters with history of perinatal death	56	2	3.6

\* $\chi^2 = 4.33$ ;  $p < 0.05$ .

\*\*Source: Kajii and Ferrier, 1978



**TABLE 8**  
**Frequency of Chromosomal Abnormalities Diagnosed Prenatally\***

Indication for Amniocentesis	No. Cases	Chromosomal Abnormalities	%
Translocation carrier	144	21	14.6
Maternal age 35-39	457	10	2.2
Maternal age $\geq 40$	528	18	3.4
Maternal age 35+ (no breakdown)	388	13	3.4
Previous Down's syndrome	932	11	1.2
Miscellaneous	501	7	
	<u>2,950</u>	<u>80</u>	<u>2.7</u>

\*Source: Milunsky and Atkins, 1977, Table 1

Table 9

Rates of Autosomal and Sex Chromosome Abnormalities  
per 1,000 Live Births in Six Studies\*

	Autosomal Abnormalities	Sex Chromosome Abnormalities	Total Chromosome Abnormalities	Number Studied
Jacobs, et al. (1974)				
Males	3.82	3.06	6.88	7489
Females	4.44	1.83	6.26	3931
Total	4.02	2.65	6.68	11680
Friedrich & Neilson (1973) Neilson & Sillisen (1975)				
Males	6.08	3.12	9.20	5761
Females	5.38	2.04	7.43	5387
Total	5.74	2.60	8.34	11148
Sergovich, et al. (1969)				
Males	0.94	4.69	5.63	1066
Females	3.94	0.	3.94	1015
Total	2.40	2.40	4.81	2081
Hamerton, et al. (1975)				
Males	2.37	1.67	4.04	7176
Females	4.44	1.04	5.47	6763
Total	3.37	1.36	4.73	13939
Lubs & Ruddle (1970)				
Males	2.30	3.22	5.51	2176
Females	2.76	1.84	4.59	2177
Total	2.53	2.53	5.05	4353
Walzer & Gerald (1977)				
	3.78	2.33	6.11	13751
<u>TOTAL</u>				
Males	3.71	2.59	6.30	37779
Females	4.49	1.51	6.00	19173
Males & Females**	4.03	2.20	6.23	43201

\*Source: Hook and Hamerton, 1977, Table 6

\*\*Excluding Walzer & Gerald, 1977

Table 10

## Malformations Attributed to Multifactorial Inheritance. \*\*

CONGENITAL MALFORMATIONS	INCIDENCE IN GENERAL POPULATION (%)	RECURRENT RATE AMONG RELATIVES (%) <sup>a</sup>			
		SIB-LINGS	OFF-SPRING	PARENTS	MONO-ZYGOTIC TWIN
Cardiac defects:					
Atrial septal defect	0.1	3.3	2.5	3.5	
Patent ductus arteriosus	0.06	2.3	2.8		
Tetralogy of Fallot	0.03	2.0	4.2		
Cleft lip & palate:					
Whites	0.08	3.9	3.5		31
Blacks	0.04				
Navajos	0.20				
Japanese	0.17				
Cleft palate					
Whites	0.05	3.0	6.2		40
Blacks	0.04				
Navajos	0.03				
Club foot (talipes equinovarus)	0.1	2.9			33
Dislocation of hip, congenital	0.07	4.3			35
Hypospadias					
Whites	0.6	7.0		6.0 <sup>†</sup>	
Blacks	0.2				
Legg-Perthes disease	0.08	3.9			
Meningo-myelocele, anencephaly, encephalocele					
Whites	0.4 <sup>‡</sup>	5.2	2.3		21
Jews	0.14 <sup>‡</sup>				
Blacks	0.08				
Pyloric stenosis	0.06				
	0.2	3.2	16.2 <sup>¶</sup> 4.6 <sup>  </sup>		22

<sup>a</sup>Data collected from many sources in different countries. It should be noted that recurrence rates vary in different countries.

<sup>†</sup>South Wales (U.K.)

<sup>‡</sup>Boston.

<sup>§</sup>Fathers.

<sup>¶</sup>If mother affected.

<sup>||</sup>If father affected.

\*\*Source: Holmes, 1976

TABLE 11. Reported Incidence of Selected Malformations<sup>a</sup>

Author	Location and Time of Study	Methods of Study	Total Births	Rate Per 1,000 Births						
				Major Malform.	Anen-cephaly	Spina Bifida	Cleft Lip +/— palate	Rectal Auresia	Club Foot	Down's Syndrome
Gittelsohn and Milham (1965)	Upstate New York 1950-60	Birth, death, stillbirth cert.	2,048,122	13.1	.73	.99	1.10	0.15	1.32	.38
Silberg, et al (1966)	Missouri 1953-64	Birth cert.	1,135,156 (livebirths)	7.4	.22	0.63	1.98	0.17	1.31	—
Ivy (1963)	Pennsylvania 1956-60	Birth cert.	1,240,540 (livebirths)	11.4	0.26	0.64	1.12	0.14	1.69	0.35
Kallen (1968)	Sweden 1964-66	Hospital reports	159,500	10.6**	0.37	0.72	1.24	0.29	1.06	—
Banister (1970)	Canada*** 1966-69	Physician reports, death, stillb. cert.	380,577	—	0.76	1.20	1.48****	0.25	1.99	0.78
Smithells (1968)	Liverpool, England 1960-64	Hospital, midwife, and clinic reports	91,176	23.9	3.14	3.36	1.05	—	2.65	1.43
Leck, et al (1968)	Birmingham, England 1950-59	Hospital & necropsy reports, death & stillbirth cert.	190,236	19.0	2.41	2.36	1.25	0.36	4.25	1.06
Neel (1958)	Hiroshima, Kure, Nagasaki, Japan, 1948-54	Birth attendant reports; physician examinations	63,796	10.2	0.63	0.20	2.13	0.24	1.07	—
Flynt, et al (unpublished)	Atlanta, Ga. 1968-69	Hospital records, death, stillbirth cert.	40,109 White 14,570 Negro	17.4	1.32	1.27	0.89	0.45	3.37	0.75
				13.5	0.41	0.82	0.69	0.27	1.58	0.67

— Indicates not given

\*\*Selected defects

\*\*\*Manitoba, Alberta, New Brunswick

\*\*\*\*Cleft palate and lip  
Taken from Flynt et al. (1970).<sup>a</sup>Source: Sholtz et al, 1976, Table 11



Table 12

Malformations with Frequency of Five or More per  
10,000 Births, in Whites and Negroes and  $\chi^2$  Test <sup>a</sup>

<u>Malformations</u>	<u>Rate per 10,000</u>		<u><math>\chi^2_{(1)}</math></u>
	<u>Whites</u>	<u>Negroes</u>	
<u>Major</u>			
Anencephaly	9.9	2.4	10.33**
Microcephaly	13.2	19.5	2.57
Hydrocephaly	13.7	13.1	0.00
Macrocephaly	10.8	5.2	4.19*
Craniosynostosis	6.2	2.8	2.51
Abnormal separation of sutures	9.5	24.7	15.55***
Meningomyelocele/meningocele	6.6	6.8	0.01
Absence or hypoplasia of fingers	5.0	4.4	0.01
Absence or hypoplasia of toes	5.0	5.2	0.01
Torticollis	16.1	9.9	3.18
Vertebral abnormality	10.8	8.0	0.76
Adduction or contracture of hip	33.5	9.2	33.62***
Congenital dislocation of hip	39.7	7.6	53.42***
Talipes-equinovarus	30.6	37.8	1.65
Metatarsus adductus	151.5	255.5	65.93***
Talipes calcaneovalgus	29.8	39.8	3.25
Scoliosis, lordosis, kyphosis	4.6	10.7	5.35*
Cataract	9.5	9.2	0.00
Cleft palate	12.4	9.6	0.68
Cleft lip	14.5	7.2	5.49*
Micrognathia	12.8	3.2	13.31***
Pectus excavatum	36.8	6.4	52.39***
Hypoplasia of lung	7.0	19.9	14.07***
Cardiac enlargement	23.6	18.3	1.41
Patent ductus arteriosus	6.6	8.8	0.48
Atrial septal defect	5.4	5.6	0.01
Ventricular septal defect	12.0	9.6	0.48
Pyloric stenosis	32.3	8.4	34.01***
Inguinal hernia	127.9	148.8	3.79

Table 12 (continued)

Umbilical hernia	11.2	14.7	0.94
Hypospadias	45.5	37.8	1.60
Undescended testes, bilateral	22.8	14.7	3.86*
Urethral meatal stenosis	7.5	19.5	12.30***
Hydroureter, megaloureter	9.5	7.6	0.30
Cystic kidney	5.4	7.6	0.60
Cavernous hemangioma	101.4	45.8	51.86***
Down syndrome	12.0	9.6	0.48
<u>Minor</u>			
Pilonidal sinus	25.3	15.1	5.81*
Polydactyly	15.7	138.9	238.19***
Syndactyly	41.8	13.5	35.04***
Abduction of foot	7.4	8.0	0.00
Abnormal fingers or toes	16.1	5.2	13.05***
Nasolacrimal duct stenosis	17.0	9.6	4.60*
Low-set ears	13.2	25.9	9.35**
Deformed pinna	57.5	58.9	0.02
Branchial cleft anomaly	27.3	163.1	236.17***
Preauricular skin tag	5.0	8.3	1.64
Cleft uvula	14.1	6.0	7.35**
Cleft gum	9.5	43.8	52.43***
Malformation of epiglottis and larynx	5.4	6.0	0.01
Delayed teeth eruption	12.8	49.8	52.02***
Undescended testes, unilateral	42.6	36.6	0.99
Fusion or adhesions, labia minora or majora	14.9	14.7	0.00
Strawberry/port-wine hemangioma	355.2	99.9	363.83***
Hairy pigmented nevus	32.3	58.5	18.04***
Supernumerary nipples	9.1	113.8	215.84***
Café-au-lait spots	34.0	114.2	105.70***

\*  $P < 0.05$ \*\*  $P < 0.01$ \*\*\*  $P < 0.001$ Yates' correction for continuity was used in computing  $\chi^2_{(1)}$ <sup>a</sup>Source: Myrianthopoulos and Chung, 1974, Table 9

Table 13

Percentage of Major and Minor Malformations in Births (Including Fetal Deaths and Live Births Followed Through First Year of Life), by Race and Sex\*

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	White			Black		
	<u>male</u>	<u>female</u>	<u>total</u>	<u>male</u>	<u>female</u>	<u>total</u>
All major	10.1	6.7	8.5	10.3	6.5	8.4
All minor	7.3	7.6	7.5	10.0	9.2	9.6

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\*Source: Myrianthopoulos and Chung, 1974, Table 4

Table 14

Frequency of Chromosome Anomalies Among Spontaneous Abortions\*, Stillbirths, and Live Births at Various Intervals Subsequent to Implantation.

Weeks Post- Implantation	1	2	3	Anomalies Total (%)
0				95 <sup>a</sup>
1-6	724/1097			66
7-11	25/108	205/425		43
12-17		62/284		22
18-24		10/196		5
25-birth			17/283	6
live births			247/43,558	.6

Sources: (1) Boué and Boué, 1976; (2) Creasy, Crolla and Alberman, 1976;  
(3) Alberman and Creasy, 1977.

\*spontaneous abortions (0-24 weeks); stillbirths (25 weeks-birth).

<sup>a</sup>author's estimate based upon figure of 78% reported by Boué and Boué (1976) for first week post-implantation (second week of development)



Table 15

## Number of Chromosome Abnormalities Expected

Weeks Post- Implantation	Number of Deaths (and Live Births) per 1,000 Implantations <sup>1</sup>	Per 1,000 Implantations		Number of Chromosome Abnormalities per 1,000 Implantations
		Proportion of Chromosome Abnormalities	Abnormalities	
0	391	x	.95	= 371.5
1-6	94	x	.66	= 62.0
7-11	40	x	.43	= 17.2
12-17	14	x	.22	= 3.1
18-24	5	x	.05	= .2
25-birth	7	x	.06	= .4
live births	449	x	.006	= 2.7
total	1,000			457.1

<sup>1</sup> Estimates using linear interpolation in Table 2 - Examples: 391 = 1,000 x (27/69); 94 = 1,000 x [(5.0 x 1/2 x 2.9)/69]

<sup>2</sup> See Table 14

Table 16

Rates (%) of Spontaneous Abortions Occurring Subsequent to a Previously Karyotyped Spontaneous Abortion, Stratified by Karyotype of Previous Abortion, by Maternal Age, and by Obstetrical History Prior to Karyotyped Abortion\*

Obstetrical History Prior to Karyotyped Abortion	<u>Prior Abortion with Abnormal Karyotype</u>		<u>Prior Abortion with Normal Karyotype</u>	
	<u>Maternal Age ≤ 30 yrs.</u>	<u>&gt; 30 yrs.</u>	<u>Maternal Age ≤ 30 yrs.</u>	<u>&gt; 30 yrs.</u>
No Pregnancy	13.3%(83)	13.3%(15)	15.6%(40)	16.7%(6)
Delivery(ies) Only	7.3%(41)	7.7%(26)	19.2%(16)	33.3%(9)
Abortion(s) and Delivery(ies)	23.0%(27)	24.0%(25)	38.9%(18)	33.3%(6)
Abortion(s) Only	14.3%(42)	41.5%(20)	23.3%(31)	12.5%(8)

( ) Number of conceptions

\*Source: Boue et al., 1973, Table 4

Figure 1.\*

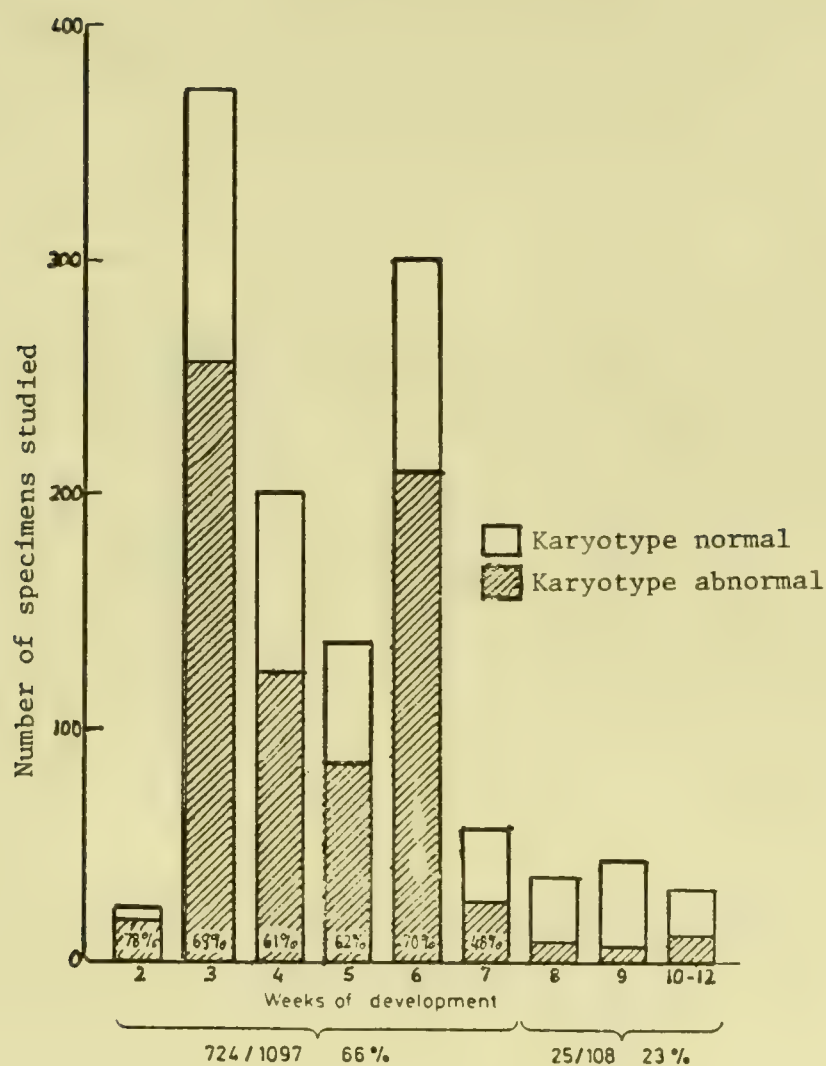


Fig. 1. Frequency of chromosomal anomalies in abortuses in relation to developmental arrest (Boué and Boué, 1974)

\*Source: Boué and Boué, 1976

Figure 2

Operating characteristic for studies of the frequency of human chromosome abnormalities among blastocysts derived from in vitro fertilization, assuming a rate of  $r_1 = 50\%$  in vivo

$$\alpha = 0.05 \quad (2.5\%)$$

Power (1- $\beta$ )

SAMPLE SIZE (n)

10 20 30 40 50 60 70 80 90 100 150 200 300 500 1000 2000 5000 10000

 $r_2 = 90\%$  $r_2 = 80\%$  $r_2 = 70\%$  $r_2 = 60\%$ 

$r_2(\%)$	R	relative risk
60	1.2	
70	1.4	
80	1.6	
90	1.8	

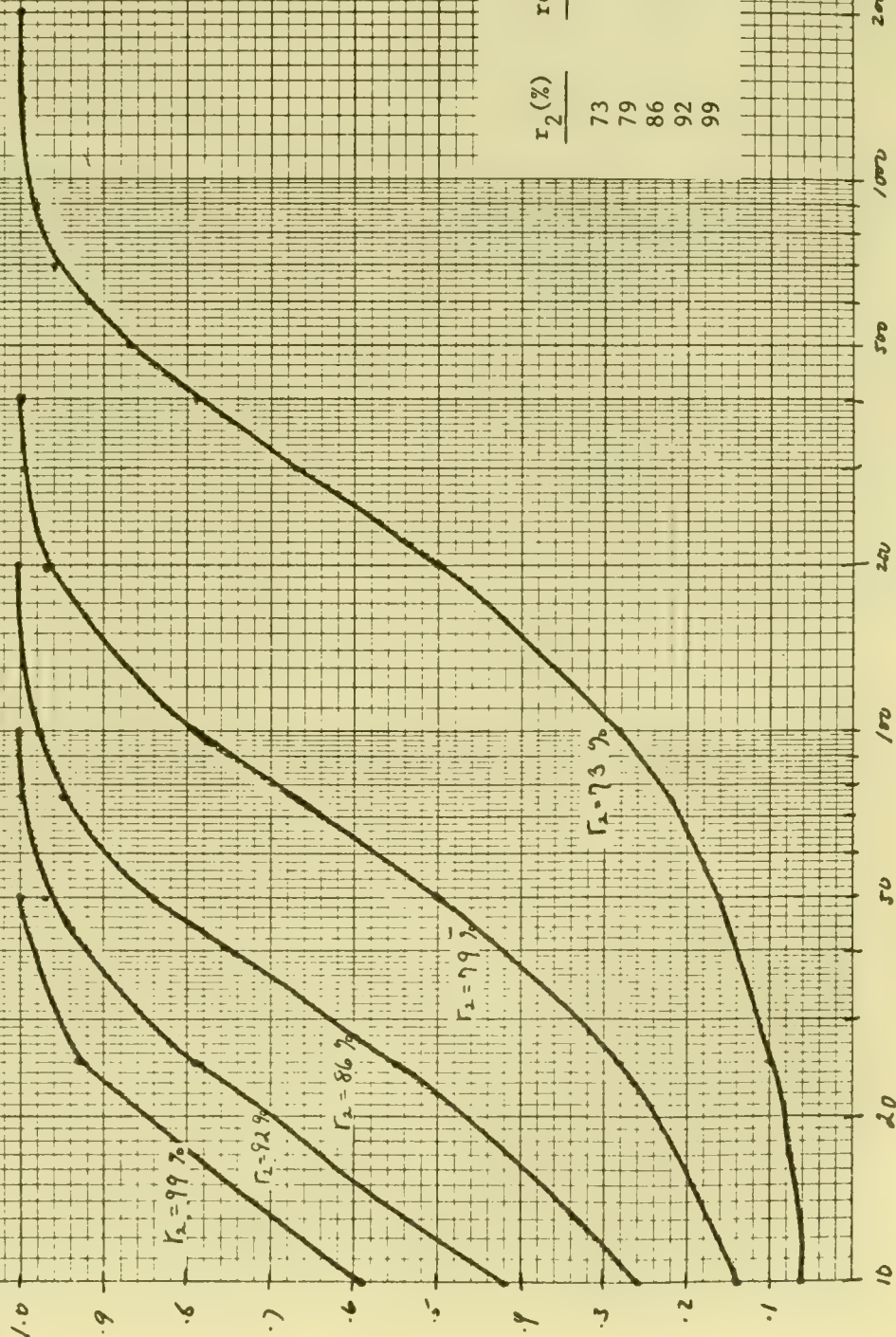


Power (1- $\beta$ )

Figure 3

Operating characteristic for studies of the frequency of human chromosome abnormalities among spontaneous abortions which occur 1-6 weeks after an implantation deriving from in vitro fertilization, assuming a rate of  $r_1 = 66\%$  in vivo

$\alpha = 0.05$  (2-sided)



Power (1- $\beta$ )

Figure 4

Operating characteristic for studies of the frequency of spontaneous abortion which occurs during the interval 1-12 weeks after an implantation deriving from in vitro fertilization in humans, assuming a rate of  $r_1=20.7\%$  in vivo

$$\alpha = 0.05 \quad (2\text{-sided})$$

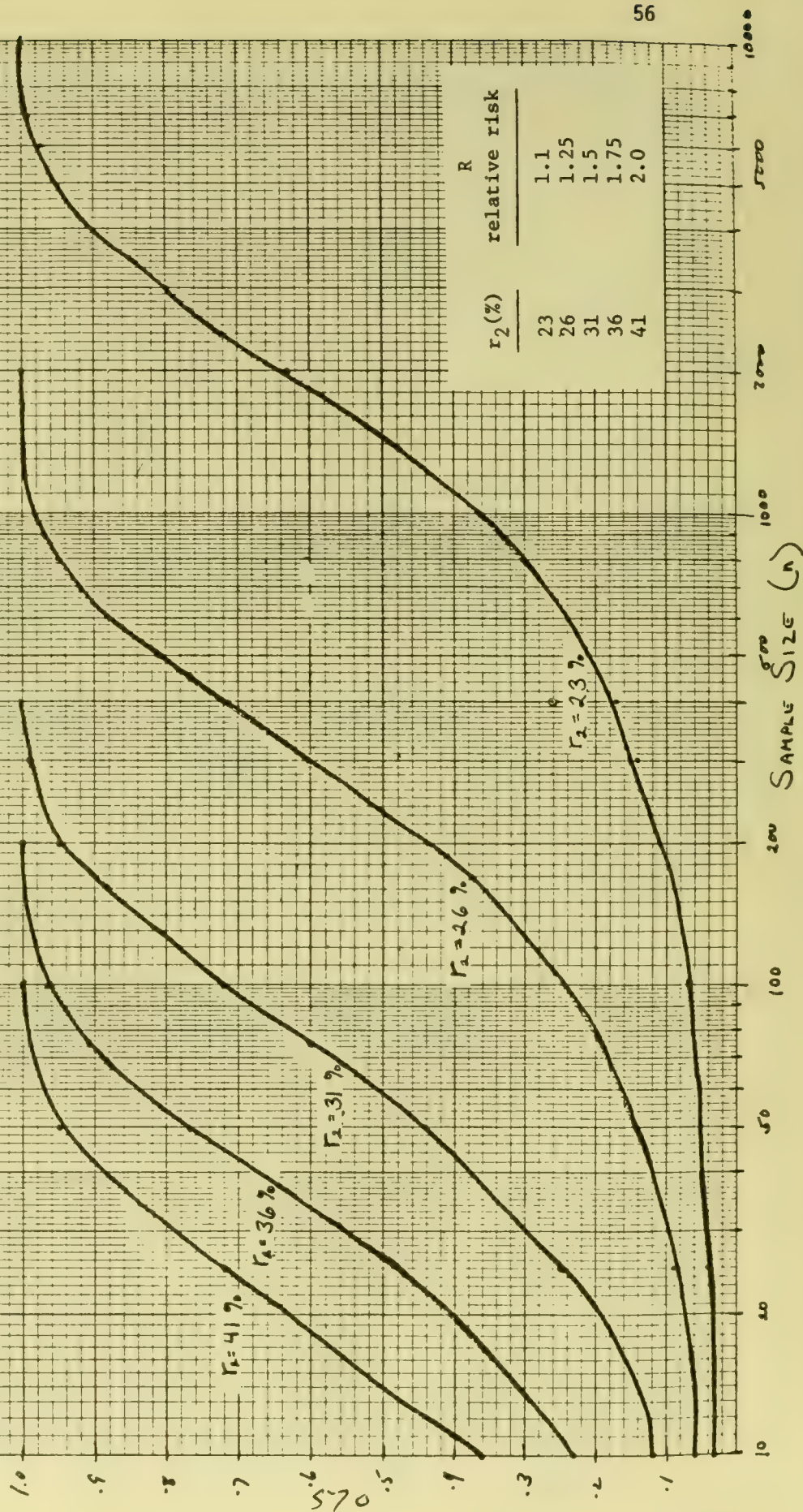




Figure 5  
Operating characteristic for studies of the frequency of major malformations occurring at birth and during the first year of life in children conceived through in vitro fertilization, assuming a rate of  $r_1 = 8.5\%$  in vivo

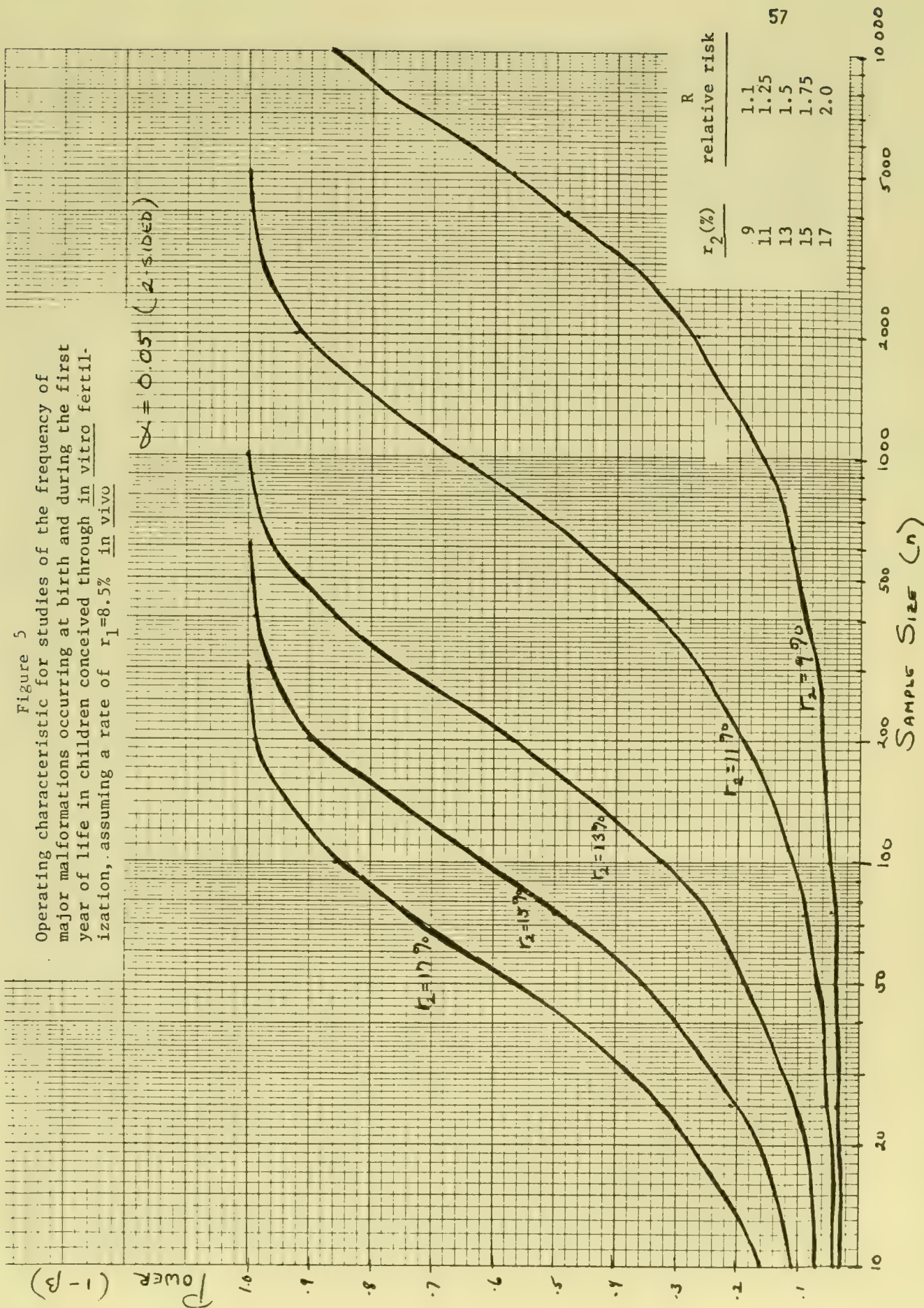


Figure 6

Operating characteristic for studies of the frequency of chromosome abnormalities in live births resulting from in vitro fertilization, assuming a rate of  $r_1 = 0.62\%$  in vivo

$\alpha = 0.05$  (2-sided)

Power  $(1 - \beta)$

0.1

$r_2 = 6.2\%$

$r_2 = 3.1\%$

$r_2 = 1.86\%$

$r_2 = 1.24\%$

$r_2(\%)$	R relative risk
1.2	2.0
1.9	3.0
3.1	5.0
6.2	10.0

SAMPLE SIZE (n)

10 50 100 200 500 1000 2000 5000 10000



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### III

#### LEGAL ISSUES





LEGAL ISSUES CONCERNING IN VITRO FERTILIZATION

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Introduction

The Department of Health, Education and Welfare (HEW) could play several roles in connection with human in vitro fertilization (IVF).<sup>1/</sup> First, HEW could participate directly in IVF research under the auspices of government entities such as the National Institutes of Health or could provide IVF health care services to eligible recipients in government hospitals and clinics such as those run by the Public Health Service or Indian Health Service.<sup>2/</sup> Second, HEW could, through its various grant and contract programs, provide funds for state, local and private research efforts.<sup>3/</sup> Third, HEW could provide Medicaid reimbursement to participating states for the cost of IVF health care services.<sup>4/</sup>

The purpose of this Memorandum is to discuss some of the legal issues that HEW may wish to address in its determination whether to conduct and/or support IVF research or health care programs and in its creation of a regulatory scheme under which any such programs would be operated. The discussion is by no means intended to be exhaustive, but rather to highlight the key issues and the factors that are likely to influence their resolution.

Section I summarizes the current status of existing federal and state law regarding IVF. Section II addresses whether and to what extent the use of IVF for procreative ends may be constitutionally prohibited or regulated. Section III discusses the prohibition or regulation question in relation to IVF research not intended or likely to produce live birth. Finally, Section IV discusses the nature and extent of the federal government's potential liability in tort suits for damages that might arise in the course of IVF research or health care programs.

I. Status Of Existing Federal And State Law  
Regarding IVF.

A. Federal Law.

Neither the Federal Constitution nor any existing federal statute appears to prohibit HEW from conducting or supporting IVF programs.<sup>5/</sup> To the contrary, direct participation by HEW in IVF programs, the funding of private, state, and local IVF research programs, and the provision of Medicaid reimbursement for IVF services all appear to fall within HEW's statutory authority.<sup>6/</sup>

HEW's involvement with IVF is, however, subject to current administrative limitations. The standards set out in HEW's general regulations regarding the protection



of human subjects apply to any IVF research, development, and related activities conducted by HEW or funded by HEW grants or contracts.<sup>7/</sup> These regulations "impose additional duties and responsibilities on investigators and research institutions over and above those generally imposed by statute and common law."<sup>8/</sup> They include procedural and substantive safeguards for human research subjects, and contain, for example, specific, detailed requirements for the securing of consent.<sup>9/</sup>

HEW considered whether to promulgate additional regulations specifically addressed to IVF research at the time that it formulated regulations concerning research projects that involve fetuses and pregnant women.<sup>10/</sup> The Department elected to require Ethics Advisory Board review of every IVF research proposal:<sup>11/</sup>

No application or proposal involving human in vitro fertilization may be funded by the Department or any component thereof until the application or proposal has been reviewed by the Ethical Advisory Board and the Board has rendered advice as to its acceptability from an ethical standpoint.  
45 C.F.R. § 46.204(e).

In the notice of proposed rulemaking issued regarding the fetal research regulations, HEW spelled out in some detail the factors to be considered by the Board:

With respect to the fertilization of human ova in vitro, it is expected that the Board will consider the extent to which current technology permits the continued development of such ova, as well as the legal and ethical issues surrounding the initiation and disposition of the products of such research.

With respect to implantation of fertilized human ova, it is expected that the Board will consider such factors as the safety of the technique (with respect to offspring) as demonstrated in animal studies, and clarification of the legal responsibilities of the donor and recipient parent(s) as well as the research personnel. 39 Fed. Reg. 30650 (1974).

While the notice of proposed rulemaking and the preamble to the fetal research regulations assert that those regulations are silent regarding IVF except for their review requirements,<sup>12/</sup> one regulation appears to require that "[a]ppropriate studies on animals and nonpregnant individuals" must be completed before any IVF research is permitted<sup>13/</sup> -- a requirement that would appear to set a standard for the Ethics Advisory Board to follow. In any event, the specific requirements applicable to IVF programs conducted or funded by HEW remain to be addressed in future regulations.<sup>14/</sup>

B. State Law.

Even though federal law does not prohibit HEW from conducting or supporting IVF programs, the operation of any such programs could be affected by state law.<sup>15/</sup> To

date, no state appears to have enacted a statute that deals specifically with IVF. But two areas of state law touch upon problems similar enough to those likely to be encountered in the context of IVF as to warrant preliminary comment.

The first of these areas is artificial insemination. To our knowledge, approximately one-third of the states have passed statutes dealing with one or more aspects of artificial insemination.<sup>16/</sup> Because these statutes do not appear to have been drafted with IVF in mind, courts are unlikely to conclude that they control the resolution of the myriad problems presented by IVF. Nonetheless, state legislatures and courts are likely to view the statutory and case law of artificial insemination as the closest analogy to IVF. Accordingly, the treatment of such matters as the legal status of resulting offspring, selection of donors and participants, physician liability, and record keeping in the context of artificial insemination may be carried over to IVF. For this reason, the law of artificial insemination is discussed at several points in this Memorandum.

A second area of state law that may have some threshold interest relates to fetal experimentation. Virtually all states have enacted at least some restrictions on such experimentation.<sup>17/</sup> Whether these restrictions

extend to IVF experimentation may depend on whether under state law the terms of the particular statute would be found to encompass ex utero blastocysts.<sup>18/</sup> The language of some state statutes plainly would not cover them.<sup>19/</sup> In other cases, it is not as clear that such terms as "fetus," "live unborn children," and "product of human conception" do not include unimplanted blastocysts.<sup>20/</sup> Because the statutes appear to have been enacted with abortion and not IVF in mind,<sup>21/</sup> it seems unlikely that these terms would be construed so broadly. One cannot, however, definitely rule out that possibility.

Even if some states were to prohibit IVF, and even if such prohibitions were deemed constitutional, that would not preclude HEW from conducting or supporting IVF research or health care programs in states that had not done so. Thus, at least for the foreseeable future, the existence of isolated state prohibitions would not appear critical to the determination whether HEW should conduct or support IVF programs and whether guidelines or regulations governing them should be promulgated.



II. Constitutional Limitations On Governmental Prohibition Or Regulation Of IVF Where The Procedure Is Intended And Expected To Produce Live Birth. <sup>22/</sup>

Government (state or federal) regulation of many aspects of medical care may be constitutionally justified if the government can assert a "rational" basis for the regulation.<sup>23/</sup> That is, the regulation is constitutional if it is "'rationally related' to a 'constitutionally permissible' purpose."<sup>24/</sup> However, when the regulation infringes upon a fundamental right protected by the Constitution, the government must justify its regulation by the far more stringent showing that the regulation is narrowly drawn to meet a "compelling" state interest. As the Supreme Court has recently noted in striking down a state restriction on the distribution of contraceptives, "regulations imposing a burden on [a fundamental right] may be justified only by compelling state interests, and must be narrowly drawn to express only those interests."<sup>25/</sup>

A determination of the constitutionality of a governmental regulation that restricts the use of IVF as a method of procreation would therefore turn on an analysis of the following factors: (1) does an individual have a fundamental right to resort to IVF for procreative ends; (2) does a given governmental restriction infringe upon that right; (3) if a fundamental right is infringed, is the

governmental interest underlying the restriction sufficiently compelling to justify the infringement; and (4) if no fundamental right is infringed, is there a rational basis for the restriction.

A contention that there is a fundamental right to employ IVF for procreative ends will most likely be based on those Supreme Court decisions that have afforded constitutional protection to certain privacy interests. In a long line of cases the Court has held that the individual is afforded a right of personal privacy that encompasses "the interest in independence in making certain kinds of important decisions."<sup>26/</sup> Based upon this right of personal privacy, the Court has held that an individual may, without unjustified governmental interference, make decisions relating to marriage,<sup>27/</sup> procreation,<sup>28/</sup> contraception,<sup>29/</sup> abortion,<sup>30/</sup> family relationships,<sup>31/</sup> child rearing,<sup>32/</sup> and "the decision whether or not to bear or beget a child."<sup>33/</sup>

A proponent of the view that IVF should be accorded constitutional safeguards could argue that a fundamental interest to utilize the procedure can be found in one of three zones of privacy that have been given constitutional protection: (1) the right to be free from unwarranted governmental interference with procreative potential; (2) the right to decide whether to bear or beget a child; and (3) in the marital context, the right of marital privacy.

Part A below examines the cases that have established the rights referred to in the preceding paragraph to determine whether the cases are sufficiently broad to encompass a right to IVF. Proceeding on the assumption that constitutional protections would be extended, at least in some of the circumstances in which IVF might be used, Part B explores factors that might weaken or strengthen an individual's claim that there is a fundamental right to use IVF for procreative ends.

The resolution of the fundamental rights issue does not, however, conclude the constitutional analysis. Any constitutional challenge to a governmental restriction on IVF will invite some degree of judicial scrutiny into the legitimacy of the governmental justification for the restriction. If, on the one hand, a fundamental right to IVF exists, but is not infringed by the restriction, or if no fundamental right is found, the restriction would be tested against a rational basis standard. If, on the other hand, a governmental restriction on IVF were found to infringe upon a fundamental right, the restriction would be constitutional only if it could be shown to be necessary to further a compelling state interest, and to be narrowly drawn so as to express only that interest. Part C examines the standards of scrutiny to which various potential governmental restrictions of IVF

are likely to be subjected and explores possible governmental interests that might be proffered as satisfying either the rational basis or compelling state interest standards.

A. Constitutional Bases For The Contention That There Is A Fundamental Right To IVF.

1. The Right To Procreation.

In Skinner v. Oklahoma, 316 U.S. 535, 541 (1942), the Supreme Court recognized that "one of the basic civil rights of man" is the right to remain free of unwarranted governmental interference with one's procreative capabilities.<sup>34/</sup> Proponents of IVF could argue that IVF allows for the fulfillment of an individual's procreative capabilities and that any unwarranted governmental interference with a decision to utilize IVF would violate the basic civil right recognized in Skinner (hereinafter referred to as "the right to procreation" or "procreation rights").

But it is by no means clear that Skinner should be read so broadly. Obviously, the Court that decided Skinner in 1942 intimated no view whether there is a constitutional right to utilize a medical procedure as a procreative alternative to intercourse. Indeed, Skinner involved the narrow issue of whether the Constitution should be interpreted to



permit a state to take affirmative intrusive steps to alter by surgery an individual's biological capacity to procreate. Skinner could, therefore, plausibly be read as merely establishing a limited protection against state action that would have the unjustifiable consequence of rendering sterile an otherwise potent individual.

2. The Right To Decide Whether To "Bear Or Beget" A Child.

An individual's right to determine whether to "bear or beget" a child free of unjustified governmental interference has been given express recognition by the Supreme Court:

If the right of privacy means anything, it is the right of the individual, married or single, to be free from unwarranted governmental intrusion into matters so fundamentally affecting a person as the decision whether to bear or beget children. Eisenstadt v. Baird, 405 U.S. 438, 453 (1972).

\* \* \*

The decision whether or not to beget or bear a child is at the very heart of this cluster of constitutionally protected choices. That decision holds a particularly important place in the history of the right of privacy, a right first explicitly recognized in an opinion holding unconstitutional a statute prohibiting the use of contraceptives, . . . and most prominently vindicated in recent years in the context of contraception . . . and abortion. Carey v. Population Serv. Intern'l, 431 U.S. 678, 685 (1977).

\* \* \*

[T]he Constitution protects individual decisions in matters of childbearing from unjustified intrusion by the State. Id. at 687. 35/

Proponents of IVF could argue that the decision whether to utilize IVF is essentially a decision whether to bear or beget a child; that the nature of the IVF decision is essentially as private and personal a decision as whether to conceive a child through intercourse; and that there is no rational justification for distinguishing between the two types of decisions for the purposes of constitutional analysis.

Opponents of this view could contend that it is by no means clear that the "bear or beget" interest identified in Eisenstadt and Carey extends to IVF. Eisenstadt and Carey can plausibly be read as cases concerned only about governmental interference with the uniquely private act of sexual intercourse. In each case, the state was seeking, through a prohibition on distribution of contraceptives, to interfere with a fundamentally private decision concerning whether intercourse should result in conception. Opponents of IVF could certainly argue that the Supreme Court's principal focus in both cases was not the broad right of an individual to have a child by whatever medical means might be available, but rather the more limited right not to have the state dictate the consequences of the private act of intercourse. 36/

3. The Right To Marital Privacy.

In a situation where a right to IVF is asserted by a married couple, it is conceivable that a court might conclude that the privacy interest that protects certain marital or family decisions is sufficiently broad to protect a decision to procreate through IVF. Such a conclusion would likely be bottomed on the notion that the determination of how to bring a child into a family is similar in kind to the private family decisions that have already been afforded constitutional protection.

As the Court noted in Griswold v. Connecticut, 381 U.S. 479, 495-96 (1965), a case that struck down a statute prohibiting the use of contraceptives by married couples:

The entire fabric of the Constitution and the purposes that clearly underlie its specific guarantees demonstrate that the rights to marital privacy and to marry and raise a family are of similar order and magnitude as the fundamental rights specifically protected . . . . The fact that no particular provision of the Constitution explicitly forbids the State from disrupting the traditional relation of the family -- a relation as old and as fundamental as our entire civilization -- surely does not show that the Government was meant to have the power to do so.

Thus, proponents of IVF could argue that the right to marital privacy protects the right not only to determine whether to have a child, but also the right of the marital relationship to remain free of unjustifiable governmental interference in the decision of how to conceive that child.

It is not possible to predict with any degree of certainty whether a court would be receptive to such an argument.

\* \* \* \*

In sum, courts might conclude -- but it is by no means certain that they will conclude -- that, at least under some circumstances, the decision to employ IVF for procreative ends is sufficiently private and bears a sufficiently close relationship to the decision to procreate through intercourse that it should be afforded the same basic protections. On the other hand, courts might determine that the interest in deciding whether to utilize IVF is different in kind from the interests that have already been afforded privacy protection, and that the decided cases should not be extended to the IVF process.

B. Factors That Might Bear Upon The Recognition  
Of A Fundamental Right To IVF.

Rights to IVF would undoubtedly be asserted in a variety of circumstances. Some might bear a close relationship to the circumstances under which procreation and child-bearing rights have been developed. Others might bear only a remote resemblance. For example, unlike conception through intercourse, the IVF procedure (1) might not be necessary to achieve procreation; (2) might be utilized by a person



who may not be genetically related to the IVF child; and (3) might be utilized by a prospective mother who would not have a gestational link to the child.

Even if a court were to conclude that procreation, "bear or beget," and marital privacy rights are relevant to an analysis of IVF issues, it might nonetheless hold that an individual does not have a fundamental right to utilize IVF under all circumstances. What follows is an analysis of how the characteristics that may distinguish procreation through IVF from procreation through intercourse (necessity, genetic connection, and gestational connection) and the added factor, whether the persons seeking to employ the procedure are doing so within the institution of marriage, might bear on the inclination of courts to extend to IVF those privacy rights that have been established in the "conception through intercourse" framework. The analysis proceeds through a series of hypotheticals that focus on the significance and interplay of these distinguishing characteristics.<sup>37/</sup>

1. Utilization OF IVF By A Husband And Wife,  
Where (a) The Ovum And Semen Are Donated  
By The Husband And Wife, (b) The Blastocyst  
Is Implanted In The Wife, And (c) Procreation  
By The Couple Is Impossible Without Resort  
To IVF.
- 

This hypothetical poses the circumstance in which the strongest argument for a fundamental right to IVF

could be made. The wife is incapable of conception through intercourse but can successfully produce an ovum for an IVF procedure. The resulting child would be genetically and gestationally linked to its married parents and the pregnancy would differ from that resulting from conception through intercourse only in its method of initiation.

Although the question is not free from doubt, a strong argument could be advanced that the right to procreation recognized in Skinner extends to these circumstances. To be sure, the government would not, as in Skinner, be taking affirmative surgical steps to alter an individual's biological capacity to procreate. The government could, however, be characterized as having deprived an individual of a medical procedure that represented the individual's only opportunity to reproduce a genetic offspring within the marital relationship. From the perspective of the potential parents, it could be argued that a governmental ban on IVF would interfere with procreative capability just as surely as would a forced sterilization. That the parents have to rely on medical technology to achieve procreative potential might not be deemed by a court to be an adequate basis to distinguish Skinner.

The presence of a "necessity" factor and a genetic relationship between the parents and the IVF child might

also serve to buttress an argument for the recognition of a "bear or beget" right to IVF. In determining whether to utilize IVF, the potential IVF parents face a decision that might, again from their perspective, be considered indistinguishable from the decision faced by a couple who must decide whether to conceive through intercourse. In both cases the decision is whether to attempt to conceive a genetic offspring. A governmental preclusion against the use of IVF to achieve that end could in effect be considered a governmental determination that the couple in the hypothetical should not conceive. To be sure, the couple would be required to avail themselves of medical technology to achieve their end, but the resulting child would be as biologically and genetically related to its prospective parents as would any child conceived through intercourse. A court might well conclude that under such circumstances the couple in the hypothetical should be afforded the same right with regard to IVF as other married couples enjoy with regard to intercourse.

Courts might also be receptive to the argument that there is a marital right of privacy to resort to IVF in this situation. The hypothetical couple would be seeking to accomplish what is an essential end of many marriages -- the birth of an off-spring that is the genetic product of the marriage. Surely

the decision of a married couple concerning whether and when to accomplish that end through intercourse is entitled to constitutional protection.<sup>38/</sup> A court might well conclude that the interests of the couple in the hypothetical are similarly private and are therefore entitled to the same protection.

\* \* \* \*

In sum, the couple in this hypothetical could advance strong arguments in support of a fundamental right to IVF. Given the presence of the necessity and genetic relationship elements, the couple faces decisions that are similar to those involved in a "conception through intercourse" setting. In the light of such similarities, courts might be willing to extend traditional privacy concepts to protect the couple in making their IVF decision.

2. Utilization Of IVF By A Husband And Wife, Where (a) The Ovum And Semen Are Donated By The Husband And Wife, (b) The Blastocyst Is Implanted In The Wife, But (c) The Couple Could, If They Chose, Procreate Through Intercourse.
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The distinguishing feature of this hypothetical is that use of IVF is not necessary for the couple to achieve conception. There are a number of reasons why such a couple



might decide to use IVF: (1) IVF might permit the screening of genetic defects; (2) the couple might want to select a blastocyst that appears to have desired characteristics (brown eyes, for example); (3) the couple might want to control the exact timing of a pregnancy for career-related or other reasons; or (4) the couple might choose to resort to IVF solely out of whim.

The assertion that there is a fundamental right to IVF in the absence of necessity obviously stands on less firm footing than the assertion described in Hypothetical No. 1. The absence of necessity would seriously undermine a Skinner right to procreation claim. Since a state prohibition against unnecessary IVF would not foreclose an individual's ability to procreate, the prohibition might not be viewed as the deprivation of "a basic liberty" in the Skinner sense.

Courts might conclude that the absence of necessity also removes IVF from the rationale of the "bear or beget" decisions. Obviously, in utero conception was assumed in Eisenstadt and Carey; the question whether an individual has a right to choose alternative methods of conception was not addressed; the question whether an individual has a right to decide to use a medical procedure to initiate a pregnancy is distinct from the question whether an individual has a right

to control the consequences of intercourse; and, in the absence of a showing of necessity, an individual's interest in bearing or begetting would not appear to be seriously infringed if he were to be limited to procreation through intercourse.

On the other hand, a court could conclude that "whether" determination and "how" determinations should not be treated separately for analytical purposes under the "bear or beget" decisions. In many situations, considerations concerning the method used to achieve conception might have a bearing on and be inexorably intertwined with the decision whether to conceive. A couple might, for example, need to control the timing of a pregnancy or might feel a necessity to screen for genetically defective blastocysts. For such reasons, a court might conclude that the right to determine whether to bear or beget a child necessarily encompasses the right to determine how to conceive.

Finally, the absence of the necessity factor is likely to be of least significance (but may nonetheless be a factor) in an analysis of whether the couple in this hypothetical has a marital privacy claim. A court might conclude that the marital right to determine whether to

produce a genetic offspring cannot be invaded by the state solely on the ground that the couple's preference for the method of conception was not necessary.

\* \* \* \*

In sum, the absence of a necessity factor would appear to weaken, but does not necessarily preclude, the claim of the couple in this hypothetical that it has a fundamental right to employ IVF for procreative ends.

3. Utilization Of IVF By A Husband And Wife, Where (a) The Ovum Is Donated By The Wife, But Third Party Semen Is Used Because The Husband Is Sterile; (b) The Blastocyst Is Implanted In The Wife; And (c) Procreation By The Couple Is Impossible Without Resort To IVF.
- 

This situation would arise when a wife is incapable of properly producing an ovum for in utero fertilization and the sterility of her husband necessitates the use of the semen of a third party donor. The problem posed is whether and to what extent the absence of a paternal genetic link has an impact upon an assertion by the couple, individually or collectively, to a fundamental right to use IVF.

The question is a complex one. Unlike the earlier hypotheticals, the interests of the husband and wife may not be identical. The husband's only relationship to the procedure is to consent to its occurrence and to agree to assume

parental responsibility for the offspring. The prospective mother, on the other hand, would bear a genetic and gestational relationship to the child. What follows is an analysis of whether these different relationships have an impact upon the respective rights of the hypothetical couple to IVF.

a.     The Husband's "Procreation"  
          And "Bear Or Beget" Claims.

The husband's sterility would seem to preclude the assertion by him of any Skinner procreation rights. An IVF prohibition would in no way foreclose a procreative option that would otherwise be available to him.

The husband's sterility would also appear seriously to undermine a claim to "bear or beget" rights on his behalf. In the instant hypothetical, the husband is a nonparticipant in the potentially procreative act. He would appear to stand in no better position than would a putative adoptive parent who wishes to assert a claim to parental rights over a child who will be genetically unrelated to him.

b.     The Wife's "Procreation"  
          And "Bear Or Beget" Claims.

In contrast to her husband, the wife in this hypothetical would appear to have stronger arguments for the recognition of a fundamental interest in IVF on "procreation" or "bear or beget" grounds. Indeed, except for the non-genetic participation by her husband, the wife stands in a



position similar to the wife in Hypothetical No. 1.

A governmental prohibition on IVF would deprive the wife of her only procreative potential within the confines of her marriage. Like the wife in Hypothetical No. 1, therefore, she might for that reason have a colorable claim to a Skinner right to IVF. Indeed, for reasons developed below, one could argue that Skinner was principally concerned with procreative potential within the context of a marriage. It is not inconceivable, however, that a court might conclude that a married individual has traditionally been forced to assume the procreative limitations of his or her spouse and that Skinner, at least, does not establish a right to escape those limitations.<sup>39/</sup>

The wife might also have a reasonable "bear or beget" claim. As in Hypothetical No. 1, she would be asserting that the "bear or beget" cases extend protection to decisions relating to whether or not an individual should bear a genetic offspring. The question raised in this hypothetical is whether that claim would be weakened where the resulting child would not be genetically linked to the husband.

The answer is not free of difficulty. But it would seem that the husband's lack of a genetic connection should not necessarily serve to diminish the prospective mother's claim. The Supreme Court has strongly suggested

that "bear or beget" interests are personal to the individual asserting them:

[T]he marital couple is not an independent entity with a mind and heart of its own, but an association of two individuals each with a separate intellectual and emotional makeup.<sup>40/</sup>

It should also be noted that the wife's individual interest would be asserted in this hypothetical with the consent of her husband and in the context of a marital relationship. Her status would appear to be closely analogous to that of a wife seeking to impregnate herself, with the consent of her husband, through the use of artificial insemination, a procedure that is widely available today.<sup>41/</sup>

c. The Marital Privacy Claim.

It remains to be considered whether the couple qua couple could assert a fundamental right to IVF on a marital privacy ground. Arguments on both sides can be constructed. In the end, the marital privacy claim would be upheld or rejected depending on the court's sensitivity to the desire of a married couple to raise a family notwithstanding the sterility of the husband. Undoubtedly, such a couple has some interest in rearing a child that bears a genetic relationship to the family. One genetic link is the best that they can hope for and their only alternative is to adopt a child.

\* \* \* \*

In sum, the absence of a paternal genetic link would appear to preclude the sterile husband's procreation claim and to undermine seriously his "bear or beget" assertion. Nevertheless, his wife's procreation and "bear or beget" interests would most likely be unaffected by his sterility and the couple would appear to have a not unreasonable marital privacy claim to utilize the procedure.

4. Utilization Of IVF By A Husband And Wife, Where (a) The Semen Is Donated By The Husband, But A Third Party Ovum Is Used Because The Wife Is Incapable Of Donating An Ovum; (b) The Blastocyst Is Implanted In The Wife, And (c) Procreation By The Couple Is Impossible Without Resort To IVF.

This hypothetical differs from the preceding one in two significant respects: (1) It is the husband, not the wife, who bears the genetic link to the child (the wife's connection with the child will be only gestational); (2) Both the husband and the wife will be participants in the IVF procedure. As in the preceding hypothetical, the respective interests of the husband and wife may not be identical.

- a. The Wife's "Procreation"  
And "Bear Or Beget" Claims.

The basic question is whether a gestational link is sufficient to support "procreation" and "bear or beget" claims to a fundamental right to utilize IVF as a method of impregnation.

It is unlikely that the wife in this hypothetical could base a fundamental right argument on a Skinner procreation claim. Plainly, the wife cannot complain of a governmental interference with reproductive potential. Unless a court were to extend Skinner to encompass not only reproductive potential, but gestational potential as well, it appears doubtful that a Skinner based claim to IVF would succeed.

Similar problems would face the hypothetical wife if she were to claim "bear or beget" rights in this context. A respectable argument could be advanced in her behalf that the manner of initiating the pregnancy should not affect the fundamental interest of an individual to make decisions regarding pregnancy free of unjustified governmental intrusion -- especially when the decision is made in the context of a marital relationship, is dictated by necessity, and relates to a woman's decision whether to assume a child-bearing role within that relationship. But a court might nonetheless refuse to extend the "bear or beget" line of decisions to a woman positing only a gestational connection to a child.

b. The Husband's "Procreation"  
And "Bear Or Beget" Claims.

With respect to his procreative or "bear or beget" assertions, the husband in this hypothetical stands in the same position as the wife in Hypothetical



No. 3. The considerations discussed there would appear to apply with equal weight to an analysis of the husband's claim in the present context.

c. Marital Privacy Rights.

The marital privacy considerations raised in this hypothetical appear similar to those discussed in Hypothetical No. 3 and will not be repeated here.

\* \* \* \*

In sum, a wife who can merely posit a gestational connection to a child is unlikely to have strong procreation or "bear or beget" claims, and her inability to ovulate may also diminish her husband's right to procreation claim. As in the preceding hypothetical, however, the lack of genetic participation by one spouse will not necessarily diminish the "bear or beget" claims of the other spouse, and the couple might have a not unreasonable marital privacy claim to support a fundamental right to the procedure.

5. Same As Hypothetical Nos. 3 And 4, Except  
That The Non-participating Spouse Is Physically  
Capable Of Donating An Ovum Or Semen.

This hypothetical once again raises the question of the importance of necessity in an analysis of whether there is a fundamental right to IVF. In this situation, one consenting spouse, although biologically capable of doing so, has chosen not to participate genetically in the IVF procedure. Among the reasons why a husband or wife might choose to forego a genetic relationship with a child are: (1) the non-participating partner may be a carrier of genetic defects (negative eugenics); (2) the couple may want to utilize a donor with a "superior" genetic make-up (positive eugenics); (3) the couple may want to develop a genetically diverse family; or (4) the non-participating partner may abstain simply out of whim.

The couple in this hypothetical would be asserting a right that, on the surface at least, does not appear particularly strong. The absence of the necessity factor would, as in Hypothetical No. 2, appear effectively to preclude the assertion of a Skinner procreation rights claim in this context. The absence of necessity would also lessen the chance that a "bear or beget" or marital privacy right would be acknowledged by a court.

6. Utilization Of IVF By A Husband Or Wife  
Where (a) The Ovum And Semen Are Donated  
By Third Parties; (b) The Blastocyst Is  
Implanted In The Wife; And (c) Procreation  
By The Couple Is Impossible Without Resort  
To IVF.

This situation would arise where the married couple is biologically incapable of producing either an ovum or semen for fertilization, but is nonetheless desirous of having a child born through the pregnancy of the wife.

It is doubtful that a court would acknowledge a fundamental right to IVF under such circumstances. The husband would appear to have even a weaker claim than did the prospective father in Hypothetical No. 3. And the wife's position is not unlike that of the wife discussed in Hypothetical No. 4.

The difficult and unique question posed by this hypothetical is whether the right of marital privacy might conceivably be extended to protect a couple's decision to have the wife assume a pregnancy for the purpose of giving birth to a child who will not be genetically related to either parent. At bottom, the marital privacy right posited in this circumstance would be a claim to a right to give birth to an adopted child through IVF. It would plainly take an enormous expansion of the marital privacy decisions to support the establishment of such a right.<sup>42/</sup>

7. Utilization Of IVF By A Husband And Wife, Where (a) The Ovum And Semen Are Donated By The Husband And Wife, But (b) The Blastocyst Is, Out Of Necessity, Implanted In The Womb Of A Surrogate.
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This hypothetical parallels Hypothetical No. 1 except in the use of a surrogate to bring the blastocyst to term.

It is conceivable that a court might conclude that the use of a surrogate does not affect the fundamental interests of the husband and wife to utilize IVF. It could be contended, for example, that a government prohibition on IVF would, as in Hypothetical No. 1, foreclose the couple's only procreative option and that Skinner interests would therefore be infringed. It could also be argued that the use of a surrogate should not affect the determination whether "bear or beget" rights should be recognized -- i.e., the right to determine the method of conceiving a genetically related offspring should not be made to turn on the method of conception that is selected. Similarly, it could be asserted that, to the extent that child bearing decisions are protected by a marital privacy right, the married couple should be protected in selecting the only available method of producing a child who is genetically related to both parents.



A court could also quite logically hold, however, that there is no constitutional right to procreate through the impregnation of a woman who is not a party to the marital relationship. A court might similarly conclude that an asserted right to impregnate a surrogate is just too far removed from the right to control the consequences of intercourse to support a "bear or beget" claim. Such a court might also reason that the interest that is protected by affording a married couple a zone of privacy does not extend to decisions that so intimately involve a stranger (the surrogate) to the marriage. That is, a court could determine that a married couple cannot claim a privacy interest in a decision that involves the impregnation of a person unrelated to the marriage.

\* \* \* \*

In sum, it is impossible to predict with assurance how a court might respond to an assertion of a fundamental right by a married couple to use a surrogate carrier. Although colorable arguments can be constructed in support of such an assertion, courts might well be hesitant to extend principles that had their origin in the privacy of the act of intercourse to sustain a right to retain the services of a surrogate to bear a child.

8. Use Of Surrogates In Other Factual Circumstances.

Hypothetical No. 7 posed the circumstance in which the strongest argument for a fundamental right to utilize a surrogate in an IVF procedure could be made. There are, however, a variety of other factual circumstances involving the use of a surrogate in which rights to IVF might be asserted. Couples might, for example, seek to use a surrogate (1) where such use is not necessary to create an offspring who is genetically related to both parents, (2) where out of choice or necessity only one parent retains a genetic link to the blastocyst, or (3) where out of choice or necessity neither parent maintains a genetic link to the blastocyst. The claims to a fundamental right to IVF in these circumstances are obviously more attenuated than those posited in connection with Hypothetical No. 7 and are even less likely to be recognized, at least at the present stage of our constitutional development.

9. IVF And The Single Individual.

A single person asserting a fundamental right to utilize IVF will have to convince a court that constitutional privacy rights are intended to protect single as well as married persons. Even if the single person were to succeed in that threshold showing, he or she would, of course, still face many of the obstacles identified in the earlier hypotheticals. For example, to the extent that IVF is not

necessary, or there is no genetic or (in the case of a woman) gestational relationship to the blastocyst, the chances of success would be substantially reduced.

Single individuals asserting a fundamental interest to utilize IVF would most likely rely upon either Skinner "procreation" or Eisenstadt and Carey "bear or beget" rights. The view that Skinner establishes a broad privacy interest in both single and married persons to be free of governmental interference with procreative capabilities finds some support in Carey, where the Supreme Court observed:

While the outer limits of this aspect of privacy have not been marked by the Court, it is clear that among the decisions that an individual may make without unjustified government interference are personal decisions 'relating to . . . procreation . . . ' 43/

Skinner itself, however, suggests that the interest there at issue was the ability to procreate within the context of the marital relationship:

We are dealing here with legislation which involves one of the basic civil rights of man. Marriage and procreation are fundamental to the very existence and survival of the race. 44/

Single persons might, therefore, elect to rest their fundamental interest claim to IVF on "bear or beget" rather than Skinner grounds. As previously noted, the Supreme Court has expressly held that "bear or beget" rights apply in at least the contraception context with equal force to single individuals.

To the extent that such rights were extended to the IVF context, the claim of single persons that they have a right to IVF on "bear or beget" grounds might conceivably be sustained.

\* \* \* \*

In sum, some constitutional rights of privacy will be held to extend to single individuals. Nevertheless, the single person will still have to convince a court that he or she has a fundamental right to IVF. The considerations that have been identified in the preceding hypotheticals would pertain to a resolution of that question. The likely result is unpredictable.

C. Constitutional Bases For Prohibiting  
Or Limiting Access To IVF.

As the preceding section demonstrates, there are sensitive public policy considerations inherent in many potential uses of IVF. HEW may decide that some of these considerations are sufficiently important to warrant a prohibition in whole or in part of HEW conduct or funding of IVF programs.<sup>45/</sup> Some states may decide that they are sufficiently important to warrant outright prohibitions or restrictions on IVF itself. Such governmental action at either the federal or state level might invite constitutional challenges. This section examines the standards of judicial scrutiny to which governmental restrictions on IVF would be



subjected and the governmental interests that might be proffered in an effort to satisfy the rational basis and/or compelling state interest standard(s).

1. Standards Of Judicial Scrutiny To Which Governmental IVF Restrictions Would Be Subjected.

As noted earlier, the degree of scrutiny to which IVF restrictions would be subjected will turn on whether the challenged restrictions infringe upon a fundamental right to IVF. In the absence of an infringement of such a right, the restriction will be tested against a rational basis standard and will be upheld if it is rationally related to a constitutionally permissible purpose. If, on the other hand, an infringement of a fundamental right is found, the restriction will be upheld only if it is shown to be necessary to satisfy a compelling state interest and to be narrowly drawn so as to express only that interest.

In Maher v. Roe, 432 U.S. 464 (1977), the Supreme Court made it clear that a governmental restriction on the use of public funds to support the exercise of a fundamental right does not, without more, constitute an impermissible governmental interference with the exercise of that right. Maher involved an equal protection challenge to a state welfare department regulation that prohibited the use of state Medicaid benefits for non-therapeutic abortions. The regulation was attacked on the ground that the prohibition impermissibly infringed upon the fundamental right of women to abort. The

Court in essence held that the existence of even a fundamental right implies no correlative government obligation to fund the exercise of that right.<sup>46/</sup>

In so holding, the Court drew a sharp distinction between a governmental action that merely encourages alternative behavior and one that directly interferes with the exercise of a right:

There is a basic difference between direct state interference with a protected activity and state encouragement of an alternative activity consonant with legislative policy. Constitutional concerns are greatest when the State attempts to impose its will by force of law; the State's power to encourage actions deemed to be in the public interest is necessarily far broader. Maher v. Roe, supra, 432 U.S. at 475-76.

The Court concluded that the existence of a fundamental right "implies no limitation on the authority of a state to make a value judgment [to discourage the exercise of that right] and to implement that judgment by the allocation of public funds."<sup>47/</sup>

Maher appears to support the proposition that HEW or the states can limit the categories of IVF programs that they conduct or fund in any rational manner that they choose, so long as they place no obstacles in the path of individuals wanting to use private sources for IVF services and do not discriminate against any "suspect class."<sup>48/</sup> It is only if HEW or a state were to choose to "impose its will by force of law" -- i.e., by specifically proscribing the use of IVF

for procreative ends (either generally or selectively)<sup>49/</sup> -- that a court might require a showing that the proscription was based on a "compelling," rather than merely "rational," state interest. And, even then, such a showing would be required only if the person(s) challenging the proscription were deemed to have a fundamental right to employ IVF for procreative ends.

## 2. Governmental Interests.

In the light of the sensitive policy questions posed by IVF, HEW can be expected to consider whether categorical limitations should be placed on the availability of HEW funds for the procreative use of IVF. Should HEW determine that unrestricted access to HEW funded IVF is undesirable, HEW would have two regulatory options. First, HEW could, pursuant to the spending power of the federal government,<sup>50/</sup> directly impose access regulations. Such regulations could range from a total prohibition on use of HEW funds for IVF to regulations imposing categorical eligibility requirements. Second, HEW might determine that the considerations underlying IVF restrictions are sufficiently controversial and sufficiently subject to legitimate difference of opinion so that the decision whether to restrict HEW funding of a particular variety of IVF should be left to the individual states.

As the Maher decision indicates, the constitutionality of any governmental decision to limit HEW funding of IVF would

be upheld if the regulatory decision could be shown to further a rational governmental interest. This part examines a number of arguable governmental interests that might be proffered in support of various funding limitations on IVF and assesses whether each interest appears sufficiently strong to satisfy the rational basis standard. To the extent that a given limitation satisfies that standard, categorical access limitations imposed by either HEW or the states implementing HEW programs will likely be upheld.<sup>51/</sup> Because, however, similar governmental interests might be asserted by states in support of an outright prohibition on IVF and because a regulation on access to HEW funding might, under some remote circumstance, be deemed to have a sufficiently pervasive impact to constitute an infringement on a fundamental right to IVF, this Section also sets forth tentative evaluations as to whether each asserted governmental interest is sufficiently strong to meet the compelling state interest standard.

a. Protection Of Blastocysts.

Insofar as medical technology requires the formation and subsequent destruction of multiple blastocysts



in order to produce one blastocyst for implantation, the government might conclude that IVF entails an impermissible destruction of potential human life, and should not therefore be permitted.<sup>52/</sup> The Supreme Court acknowledged in Roe v. Wade that the question of when life begins has been the subject of considerable debate.<sup>53/</sup> It is not unlikely, therefore, that a government decision that blastocysts should not be formed and then destroyed would be considered rational.<sup>54/</sup> Any prohibition on funding or on IVF itself based on such a decision would likely withstand analysis under the rational basis standard.

It is, however, far less likely that the state's interest in protecting potential human life would be considered so strong as to constitute a compelling state interest justifying an outright prohibition of IVF by individuals who could establish a fundamental right to its use. In Roe v. Wade, the Supreme Court held that the state's interest in protecting potential human life does not become compelling until a fetus reaches the stage of "viability," defined by the Court as "the interim point at which the fetus becomes . . . potentially able to live outside the mother's womb, albeit with artificial aid."<sup>55/</sup> It seems inconceivable that any court would hold that blastocysts are in any sense

"viable" prior to the time they are discarded in the course of an IVF procedure.<sup>56/</sup> Thus, if a fundamental right to IVF were found to exist (for example, in the case of a married couple fitting within the parameters of Hypothetical No. 1), a court might well find the reasoning of Roe v. Wade controlling and invalidate a governmental prohibition of IVF in that context.<sup>57/</sup>

b. Fostering Marriage And Discouraging Illegitimacy.

Historically, courts and legislatures have fostered marriage as the preferred method of child bearing and discouraged the birth of illegitimate children. As one court explained:

The family is the basic unit of our society, the center of the personal affections that ennoble and enrich human life. It channels biological drives that might otherwise become socially destructive; it ensures the care and education of children in a stable environment; it establishes continuity from one generation to another; it nurtures and develops the individual initiative that distinguishes a free people . . . . Since the family is the core of our society, the law seeks to foster and preserve marriage. <sup>58/</sup>

HEW or the implementing states might, therefore, decide that the funding of IVF for procreative ends should be limited to married couples only.

Such a decision would in all likelihood be deemed to reflect a rational state interest. The Supreme Court has recently reaffirmed the importance of the state's interest "in

protecting 'legitimate family relationships,' . . . and the regulation and protection of the family unit."<sup>59/</sup> The Court has suggested that absent an infringement on a fundamental right, legislation which legitimately promotes that interest will be upheld.<sup>60/</sup> A measure that limited IVF to the marital context would likely be deemed to promote a legitimate governmental interest and might well withstand analysis under the rational basis standard.

It is far more difficult to assess, however, whether the state's interest in fostering the family would be considered sufficiently compelling to justify an outright prohibition of use of IVF by non-married individuals if that prohibition were deemed to infringe upon a fundamental right. In recent years contemporary attitudes toward the once widely shared view that the "family is the core of our society" have undergone change. Adultery and fornication statutes have been repealed or modified in many states. No-fault divorce has become fairly common. Only a few states appear to have enacted legislation restricting artificial insemination to married persons.<sup>61/</sup> And as noted earlier, the Supreme Court itself has acknowledged that single, as well as married, persons are entitled to rights of privacy in procreative decisions.<sup>62/</sup>

In the light of this social and legal climate, it is questionable whether the state's interest in protecting

the family would be deemed to be a sufficiently compelling interest to override a single individual's fundamental right to utilize IVF for procreative ends, should such a fundamental right be acknowledged by a court. Moreover, even a court that might conclude that the state does have a compelling interest in so limiting access to IVF might, nonetheless, strike down a blanket proscription on utilization of IVF by all single individuals. Such a court might well reason that the only compelling state interest at stake is the state's legitimate concern for the welfare of the child, and that a blanket prohibition that is not narrowly drawn to reflect ability to care for and support a child could not satisfy the rigid standards of the compelling state interest test.<sup>63/</sup>

c. Preclusion Of Eugenic Engineering.

IVF obviously has the potential for eugenic engineering. The use of donated genetic materials lends to IVF an aspect of genetic planning that the government might wish to control or prohibit. Indeed, as one commentator has noted:

For a state to leave in the hands of private parties the power of radically altering the genetic quality of the population would require an act of political self-restraint of a character unknown in human history. <sup>64/</sup>

The government would appear to have two separate grounds for controlling or prohibiting the use of donated genetic materials. First, such measures might



be deemed appropriate to prevent small groups of people from exercising genetic selection decisions that could have far-reaching effects on society as a whole. Second, the state may wish to deter individuals from using IVF as a method of producing genetically superior offspring. These considerations will be treated seriatim.

The power to determine who is a suitable donor is in essence a power to make important subjective judgments about which genetic traits society should perpetuate. If left unregulated, such judgments would likely be exercised by the doctors or hospitals involved in the IVF procedure. Indeed, this appears to be exactly what has occurred in connection with artificial insemination.<sup>65/</sup>

To the extent that IVF becomes widespread, the exercise of such judgments about desirable genetic traits might have a not insubstantial impact on the genetic composition of the population. The government might rationally conclude that it would be to society's detriment to allow any group, including the government itself, to manipulate in this manner the future genetic composition of society. Therefore, HEW or the implementing states might seek to preclude funding of or prohibit IVF for procreative ends when donated genetic materials are used.

To date no court appears to have assessed the state's interest in regulating conduct on "eugenic engineering" grounds. A

correctly articulated concern about genetic manipulation of the population might well be acknowledged to be a rational state concern. It is conceivable, but by no means clear, that the concern would be deemed to be sufficiently compelling so as to justify an outright prohibition of IVF.

The government might also be concerned about the availability of IVF as a method of family genetic planning. The use of donated genetic material for the purpose of producing a superior genetic offspring might be deemed by the government to be a socially undesirable method of procreation. It is, again, difficult to assess the weight that a court might attach to such an interest.

Unlike a funding prohibition founded on concern over the implications of the donor selection process, a funding preclusion on the use of donated material based on genetic planning grounds need not necessarily be absolute. The government's interest in deterring the use of IVF as a method of family genetic planning might be deemed to be satisfied by a prohibition on the non-necessary use of donated materials. A more broadly-drafted prohibition that would encompass individuals acting out of necessity (see Hypothetical Nos. 3 and 4) might not be deemed to further that interest in a rational manner and might be found to be deficient when judged against both the rational basis and the compelling state interest standards.

d. Prohibition Of Surrogate Carriers.

The use of surrogate carriers would unquestionably give rise to a host of difficult and perhaps intractable legal questions. The status of the child would be a matter of some complexity. Disputes would probably arise between "surrogate" and "IVF parents" from efforts that the prospective IVF parents would surely make to achieve maximum control over the surrogate during her pregnancy. For example, the IVF parents might wish to confine the surrogate's intake of food and drugs during gestation; or to require that the surrogate undergo a periodic medical examination, perhaps including intrusive techniques such as amniocentesis, or other methods of fetal monitoring; or to control the decision whether the fetus should be aborted during pregnancy. One commentator has suggested that such problems might be resolvable through contractual arrangements.<sup>66/</sup> But it is questionable that a court would or could enforce a contractual provision that requires a woman to abort, to refrain from a desired abortion,<sup>67/</sup> or to submit to intrusive medical procedures.

In light of these problems, HEW or the implementing states might rationally conclude that the use of surrogates gives rise to a sufficiently large number of socially undesirable problems so as to warrant a total ban on the practice.<sup>68/</sup> Indeed, these problems might well be deemed

sufficiently serious as to satisfy the compelling state interest standard and to warrant an absolute ban on the use of surrogates in all IVF procedures.

D. Additional Regulatory Considerations.

If HEW should decide to conduct or fund IVF programs intended and expected to produce live births, it will undoubtedly address regulatory concerns in addition to the ones discussed above. This section will assess a number of such concerns.

1. Health And Safety.

As was explained at the outset of this Section,<sup>69/</sup> it has been assumed throughout the foregoing analysis that IVF techniques are sufficiently advanced so as to present no undue risk of defective childbirths or harm to prospective mothers undergoing the procedure. Neither of these assumptions is necessarily correct at this stage of IVF development.

Obviously, HEW or the states could promulgate restrictions reasonably calculated to protect women from "an inherently hazardous procedure."<sup>70/</sup> In addition, if it could be shown that there is a substantially larger risk of spontaneous abortions or deformed births via IVF than in natural pregnancy,<sup>71/</sup> HEW or the states could similarly promulgate restrictions calculated to address that situation. Whether either of these concerns would be of sufficient



weight to support a total prohibition of IVF in all circumstances would depend on the actual risks involved<sup>72/</sup> and the extent to which persons affected by the prohibition were deemed to have a fundamental right to procreate through IVF.

## 2. Legal Status Of The IVF Child.

Problems concerning the legal status of children are traditionally left to the states to resolve. No state has yet enacted legislation to define the status of IVF children. It can be expected, therefore, that HEW will be reluctant to conduct or fund IVF programs intended and expected to produce live births unless it has some assurance that any resulting children will be accorded reasonable protections.

In this connection, the approach that the states have taken in the analogous area of artificial insemination may be of interest to HEW. There are two types of artificial insemination that bear close similarities to IVF. The first, called homologous artificial insemination ("AIH"), involves the use of the semen of a husband to fertilize the ovum of his wife. Since both husband and wife are genetically related to the child, AIH closely resembles the IVF procedure described in Hypothetical No. 1. The second, called heterologous artificial insemination ("AID"),

impregnates the prospective mother with the sperm of a third party donor. AID closely resembles the IVF procedure described in Hypothetical No. 3.<sup>73/</sup>

Although no case has directly addressed the issue, a number of courts have observed that AIH "creates no legal problems since the child is considered the natural child of the husband and wife."<sup>74/</sup> There appears to be no reason why courts should not be inclined to treat the analogous (Hypothetical No. 1) IVF situation in a similar fashion.

In contrast, the status of the AID child has not been so easily resolved. The states have struggled, both in legislation and in decisional law, to grapple with the issues presented. Since the state legislatures enjoy greater flexibility than do the courts, it should come as no surprise that they have had more success in addressing the issues.

The statutes that state legislatures have enacted generally provide that a husband shall be deemed to be the natural father of an AID child if he has consented to the procedure.<sup>75/</sup> A number of states additionally provide that the donor shall be deemed to have no parental or other relationship to the child.<sup>76/</sup> "Judicial confusion" appears to have marked the efforts of courts to resolve these same questions in the absence of legislative guidance.<sup>77/</sup> But

two general rules seem to emerge from those efforts: (1) The AID child has generally been held to be illegitimate in the absence of a statute dictating a contrary result. (2) A non-participating husband has nevertheless been charged with support obligations if he either (a) consented to the AID procedure or (b) ratified the procedure by knowingly accepting the AID child as his own.<sup>78/</sup>

It may well be that the most useful conclusion HEW can draw from the artificial insemination experience is that every effort should be made to clarify legal rights and responsibilities before IVF is undertaken for procreative purposes. HEW would appear to have two basic alternatives in this regard.

First, HEW might decline to fund IVF in any state that has not enacted legislation defining the parental rights and responsibilities of each of the participants in the procedure. Such an approach would have the virtue of certainty. But, on the negative side, it might greatly undercut efforts to support the development of IVF if such development is considered a worthwhile goal. The states have shown a reluctance to legislate about artificial insemination and may be similarly reluctant to legislate about the even more controversial and complex subject of IVF. This might be especially so if failure to legislate

would have the affirmative effect of cutting off federal funding of IVF and thereby deterring the practice within the state.

A second alternative for HEW might be to require that, in the absence of governing state legislation, regulation, or decisional law, all matters of parental responsibility be resolved prior to the IVF procedure through the execution of written agreements. If, for example, IVF were to be performed in a marital context, with the sperm of a third party as a prerequisite for the performance of the procedure, HEW might require that the husband consent to the procedure and agree in writing to assume paternal responsibilities for the child. Such a consent requirement is commonly found in the artificial insemination statutes that have been enacted to date<sup>79/</sup> and in the legislation proposed by various commentators.<sup>80/</sup> Similarly, if IVF were to be performed with the ovum of a third party and implanted in the prospective mother (Hypothetical No. 4), HEW might consider requiring both the prospective mother and father to agree in writing to assume parental responsibility for the child. Finally, in all cases in which donated sperm or ova are used, HEW might require that each party execute a written understanding that the donor shall be barred from asserting or being charged with parental claims.



Such requirements would not, of course, necessarily resolve the parental responsibility problems in a definitive manner. A state court might declare that questions of parental responsibility where genetic material has been donated must be resolved by reference to state adoption and common law principles and not in accordance with the provisions of a federally mandated agreement. It does, however, seem likely that a court, faced with difficult and sensitive status questions, would lend great weight to a prior statement of the obligations that each participant represented he or she would assume.<sup>81/</sup>

3. Other Topics Of Regulation.

Among other legal problems that HEW may want to consider addressing in a regulatory scheme are the following.

a. Regulation of the attending physician's role in implantation and abortion decisions. It could be argued that the attending IVF physician has unique expertise to assess the potential viability of a particular blastocyst and is in the best position to decide whether a particular blastocyst should be implanted. Similar arguments could be advanced that the attending IVF physician has unique expertise to monitor fetal development after the blastocyst is implanted and is also in the best position to make a judgment concerning abortion. The physician might therefore, by regulation, be given the sole authority to make these decisions. Such a regulation would require the prospective parents to agree in

advance to this procedure and would have the plain effect of removing from their hands the decision whether to go forward with an IVF procedure. Two questions can be raised with respect to such a regulation: (1) Would the regulation be desirable? (2) Would it be constitutional?

There are arguments that can be advanced on both sides of the question. On the one hand, it could be argued that prospective IVF parents are ill-equipped to make reasoned judgments about the progress of the IVF procedure. Prospective IVF parents will often be individuals who are incapable of conceiving through intercourse and have resorted to IVF out of near desperation to conceive a child. Although the attending IVF physician could, as he would about any medical procedure, advise such prospective parents of the risks of implantation and the prospects for success, it is possible, perhaps even likely, that many prospective parents would be emotionally resistant to discouraging advice. Therefore, it might be considered prudent to remove the implantation and abortion decisions from their hands.

On the other hand, there may be a legitimate concern that doctors engaged in the development of IVF may have interests of their own (relating to reputation or other matters irrelevant to the particular case) in assuring that children born as a result of IVF face diminished risks of genetic or other harm. They may, in short, be overly

cautious in their judgments by refusing to implant and by ordering the abortion of all but the most perfect blastocysts. For this reason, authorizing the physician to make the implantation and abortion decisions may harm rather than enhance the prospective parents' interests.

The regulations here considered would also raise difficult constitutional problems. A constitutional analysis of the regulations would turn on the resolution of two issues. (1) Does an individual have a fundamental right to make the implantation and abortion decisions? It seems clear that a woman has a fundamental right to choose whether or not to abort. It is far less certain that a couple would have a similar right to make the implantation decision. Although such a right might conceivably be acknowledged if a fundamental right to utilize IVF were established, the implantation decision would appear, on the surface at least, to be not unlike the myriad of decisions that are traditionally left to the professional judgment of attending physicians. (2) To the extent that a fundamental right to make each decision exists, would such a regulation constitute an impermissible interference with the exercise of that right? The regulation under discussion would not, of course, prohibit an individual from making such decisions when the IVF procedure has been privately funded. It would, however, require an individual

to waive that right as a condition of acceptance of government funding of the IVF procedure. It is problematical whether the government can so condition acceptance of a government benefit.<sup>82/</sup> It also appears inconceivable, in any event, that a court would require specific performance by a woman who had agreed to abide by a doctor's abortion decision and then changed her mind.

b. Record keeping. Existing regulations on fetal experimentation do not address matters of record keeping concerning the subjects of research. The imposition of a record keeping requirement would pose a significant question of whether such records should be sealed or otherwise kept from public access or even access by other parties involved. In this connection, states that have imposed record keeping requirements in the analogous artificial insemination area have required that all records be filed with prescribed state agencies and not be made available for inspection except upon court order.<sup>83/</sup>



III. Constitutional Limitations On Governmental Prohibition Or Regulation Of IVF Research Where The Procedure Is Not Intended Or Likely To Produce Live Birth.

Although IVF has been successful in at least two reported instances of live births, it appears that research dedicated to improving existing IVF procedures and to developing alternatives to them will continue.<sup>84/</sup> Other areas of research may also employ IVF. Accordingly, HEW is concerned not only with the funding and delivery of IVF care intended in each case to produce children, but also with the funding and performance of IVF research or experimentation.

As discussed in the preceding Section, HEW has broad latitude to refuse to fund a given practice or project. If HEW were to refuse to fund any IVF research, that decision might well be upheld simply on the basis of HEW's conclusion that other areas of research are more deserving of federal funding. Nevertheless, in assessing whether or not to fund IVF research, HEW should be aware of various rights that might be asserted in connection with participation in such research.

In addition, although no state has enacted a statute specifically prohibiting or restricting IVF research or experimentation as such, it is conceivable that a state might decide to do so in the future. If a substantial

number of states were to enact such statutes, they would significantly interfere with possible HEW research programs, at least until such time as their constitutionality was tested.

Accordingly, this Section of the Memorandum discusses the constitutional implications of measures prohibiting or restricting IVF in three conceptually distinguishable research situations:

- (1) Research that is conducted wholly ex utero.
- (2) Research that includes implantation solely for experimental purposes and with no intention of a resulting childbirth.
- (3) Research that includes implantation with some hope for birth.<sup>85/</sup>

This is not to suggest that these three research situations may not occur at the same time, and at the same time that IVF procedures are used with the intent and expectation of regularly producing births. For example, while some IVF procedures may be developed to the stage of reliably producing live births, researchers might wish to attempt alternative but unproven methods of blastocyst implantation.

Even if the Constitution were interpreted to require a state to permit at least some individuals -- such

as the married couple in Hypothetical No. 1 -- to utilize non-experimental IVF procedures in order to beget children, it is not at all certain that the Constitution would also be deemed to require a state to permit IVF research. The courts, of course, have never considered this question. Thus, as in the case of the constitutional limitations on governmental restrictions of non-experimental IVF procedures, it is not possible to reach any definitive conclusions about governmental authority to prohibit or restrict IVF research. It is possible, however, to outline the constitutional issues that are most likely to be raised in connection with an adjudication of the validity of the exercise of such authority.

A.     Constitutional Issues Regarding A Refusal  
          To Fund Or A Prohibition Against IVF  
          Research Conducted Wholly Ex Utero.

Various kinds of research can be envisioned that could involve IVF procedures conducted wholly ex utero. For example, research regarding optimum conditions for blastocyst culture and development might be carried out without any intent to implant such blastocysts for childbearing purposes. Experiments might be designed involving blastocyst culture in vitro for purposes wholly unrelated to reproduction research, such as testing drugs for human tissue toxicity.

Or experiments might be conducted to perfect the development of an artificial womb.

In analyzing the constitutionality of a governmental prohibition on such research, it is necessary again to consider whether the prohibition would infringe on any fundamental rights and whether the governmental justification for the prohibition is likely to be deemed sufficiently strong to support its constitutionality.

1. The Argument That Such Research Is Constitutionally Protected Qua Research.

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research has expressed the view that "there is good reason to believe that if a case arose, the Supreme Court would recognize a First Amendment 'right to research.'" <sup>86/</sup> This view is supported by some legal commentary, <sup>87/</sup> but it has not been tested in the Supreme Court. Proponents of the view that such a right to participate in research is embodied in the First Amendment rely largely on analogy to cases indicating that journalists have a constitutionally protected right to <sup>88/</sup> gather news.

It is not at all clear, however, that a researcher could assert a fundamental right to perform IVF research that



would prevail against a prohibition on such research enacted not as a device to censor scientific inquiry as such, but to prohibit as socially undesirable conduct all IVF manipulation (regardless of its purpose). In explaining its concept of what would be encompassed within a "right to research," the National Commission emphasized the limited scope of the putative "right." It was the Commission's view that although the government would not be able to restrict or regulate research "on the basis of the ideas or knowledge sought," it would nevertheless be entitled to regulate such research

on the basis of the manner in which the research is carried out. Thus, the state may not interfere with the researcher's choice of the end or topic of research, but it may regulate only the methods used in the research, in order to protect interests in health, order and safety with which unrestricted research might conflict. Such restrictions are valid if they are reasonably related to protection of non-speech interests and are not so vague and over broad that they chill the exercise of protected speech. Thus, the state may restrict research methods to protect the health or autonomy of subjects, or the safety of the surrounding community, even if, in some instances, the restrictions prevent the research altogether. 89/

This analysis appears to be in accord with traditional First Amendment principles. 90/ The newsgathering cases

do not appear to recognize a special press right to access to events that the public may not witness.<sup>91/</sup> Similarly, it is reasonable to conclude that researchers have no special right to participate in procedures designed to advance scientific knowledge if participation in such procedures would be prohibited to laymen on legitimate public policy grounds.<sup>92/</sup> Moreover, neither the principles established in the newsgathering cases, nor other established principles, appear to support an argument that a prohibition against certain methods of experimentation (or other conduct) must be specially justified by a compelling governmental interest simply because an individual wishes to participate in the activity as an incident to an exercise of free speech rights.<sup>93/</sup>

In this light it seems likely that a potential IVF researcher or potential IVF research participants could not successfully assert a "fundamental" First Amendment interest in ex utero IVF research that could be outweighed only by a compelling governmental prohibition against such research -- at least if the governmental prohibition were directed not against the development or reporting of scientific knowledge as such, but against the formation, manipulation, and destruction of blastocysts.

2.    The Argument That Individuals Are  
      Entitled To Make Their Own Private  
      Decisions, Without Governmental  
      Interference, About Whether To  
      Participate In Such Research.

Even if there is no constitutionally protected fundamental interest to perform or participate in ex utero IVF research qua research, the donors of the reproductive cells used in such experiments might contend that they have a constitutionally protected fundamental privacy right to control the use and manipulation of their own reproductive materials. And they might further contend that this right entitles them to participate in such research without interference from the government in the absence of a contrary compelling governmental interest.

In Roe v. Wade, the Supreme Court recognized that the Fourteenth Amendment includes a "concept of personal liberty and [restriction] upon state action" that is "broad enough to encompass a woman's decision whether or not to terminate her pregnancy."<sup>94/</sup> It might be argued that if women have a constitutionally protected fundamental right to abort, even though that right entails the destruction of a fetus, then women and men must also possess a constitutionally protected fundamental right to dedicate the use of their reproductive cells to IVF research.

It is doubtful, however, that a court would adopt the argument that an individual possesses a constitutionally protected right to dedicate his reproductive cells to IVF research (or to use them in any way other than to beget children). The privacy interests protected in Roe and in other privacy cases concern matters of substantial and tangible impact on the individuals asserting those interests. Critical to the holding in Roe, for example, was the fact that only by aborting may a woman avoid the burdens of pregnancy on herself.<sup>95/</sup> By contrast, women and men donating reproductive cells for ex utero IVF research have no similar interest. Moreover, after their reproductive material has been donated for research purposes, the donors have no significant relationship with the research materials that relates to any procreative desires, to any decision of theirs to bear or beget children, to any right to the privacy of their marriage, or to any other similar interest.

For this reason, Roe and the other privacy cases seem largely inapposite. When donation of reproductive material is made to research, the participants in the research are acting outside the areas of privacy addressed in those cases. And even if the use of reproductive materials in the procreative context may ordinarily be beyond governmental interference, it can be strongly argued that outside



that context the constitutionally protected fundamental privacy interest in such control no longer applies.<sup>96/</sup>

Potential IVF research participants might, of course, contend that at least some IVF research is integral to perfecting techniques for child bearing purposes. But even if those, or other, individuals may have a constitutionally protected fundamental right to bear children through IVF (were it to be perfected), it does not necessarily follow that they would have a procreation, bear or beget, or marital privacy right to participate in experimentation aimed at perfecting that technique.<sup>97/</sup>

3. Governmental Interests Supporting A Refusal To Fund Or A Prohibition Against IVF Research.

The foregoing discussion suggests that a strong possibility exists that no constitutionally protected interest in ex utero IVF research could be advanced that could be prohibited only on a showing of a compelling governmental interest.<sup>98/</sup> If this is so, then any rational public interest that may be advanced in support of a refusal to fund, or a prohibition against, IVF research would be sufficient to sustain the constitutionality of such a provision.

In the case of a governmental refusal merely to fund IVF research, this constitutional test of rationality may well be satisfied simply by a reasonable administrative

determination that other research would be more useful to the government. In addition, at least two of the general governmental interests that might be advanced in support of a state prohibition against the use of IVF for procreation may also be advanced to support a governmental prohibition against IVF research, or a governmental refusal to fund IVF research.

First, the government might assert that ex utero research poses a threat to donors of reproductive materials, particularly women, and thus that safety interests justify a prohibition on such research. However, if laparoscopy is in fact a "routine" procedure and if researchers could solicit ova donors who would otherwise be undergoing laparoscopy or related procedures, thus minimizing the intrusion and attendant risk of the donation process, a court might conclude that a state's interest in prohibiting ex utero IVF research on safety grounds is very slight.<sup>99/</sup>

Second, the government might justify a refusal to fund IVF research or a prohibition against IVF research on the ground that manipulation of reproductive tissues in vitro is inconsistent with the dignity that should be afforded potential human life forms. A variety of governmental interests might fit within this description. The

government might advance the view that any kind of ex utero manipulation of reproductive materials is unacceptable. Alternatively, the government might assert that IVF research is improper not because of the manipulation of reproductive materials as such, but because potential life is artificially created with the intention to destroy it.<sup>100/</sup> Still other justifications might be advanced in connection with particular research projects. For example, the government might assert that it has an interest in prohibiting IVF research methods that include eugenic screening or recombination of human genes as inconsistent with human dignity, even while permitting other kinds of IVF research.. While it is far from certain that such interests would constitute compelling governmental interests sufficient to justify an infringement of a constitutionally protected fundamental right, for the reasons discussed in Section II they would appear to satisfy the rational basis test.

B. Constitutional Issues Regarding A Refusal To Fund Or A Prohibition Against IVF Research Involving Implantation, But With The Design Not To Produce A Child.

IVF research might also include experimentation in which a blastocyst is cultured in vitro and implanted, but with no intention to permit the blastocyst to develop

into a viable fetus. In such cases, it might be expected that the fetus or blastocyst will expire naturally. It might also be planned in advance to abort the blastocyst or fetus. As with wholly ex utero IVF research, such research may be undertaken to perfect IVF reproduction techniques, or to study other phenomena, e.g., drug toxicity.

A constitutional challenge to a prohibition against such research (or a refusal to fund it) would raise many of the same arguments and responses already considered in appraising the constitutionality of similar measures regarding wholly ex utero IVF research. For example, the arguments that might be advanced in claiming that such research is entitled to special First Amendment protection qua research appear identical to the concerns and arguments addressed in connection with ex utero research. They are accordingly unlikely to be successful. In addition, as in the case of ex utero research, it seems unlikely that the argument in favor of the existence of a constitutionally protected fundamental right to participate in such IVF research could be supported by the existing precedent dealing with procreation, bearing or begetting children, or marital privacy. When it is certain that no child will result from the research -- because it is certain either



that the fetus could not survive or that the woman carrying the fetus will abort -- then these privacy concerns seem <sup>101/</sup> inapplicable.

It is true, of course, that implantation of a blastocyst is a more personal and substantial undertaking by a woman than mere ova donation for ex utero manipulation. But such participation may still not be considered an event of the sort attended with traditional expectations of privacy and autonomy. <sup>102/</sup> Rather, these procedures may be regarded as more closely akin to participation in routine medical experiments of the sort that have long been considered <sup>103/</sup> properly subject to government regulation.

Indeed, the fact that implantation is involved may strengthen governmental interests in restricting such research. Implantation and gestation bring additional risks to the experimental procedure, and the governmental interest in protecting safety would appear to be accordingly greater. The same health and moral interests that can be advanced in prohibiting socially unacceptable forms of employment, such as, perhaps, surrogate gestation of an IVF fetus, might well be advanced to proscribe employment of participants in IVF implantation research. Finally, to the extent that an implanted blastocyst may have a greater life potential or <sup>104/</sup> entitlement to dignified treatment than an unimplanted one, the governmental interests in protecting the dignity of of potential human life may be greater in IVF research

involving implantation. Accordingly, a court might well consider a governmental restriction on IVF research involving implantation to be rationally justified even if the government did not impose similar measures regarding ex utero IVF research.

IVF research that involves implantation does, however, give rise to one additional constitutional consideration: Would a prohibition against such IVF research unconstitutionally interfere with a woman's exercising her right to an abortion? Although the matter is far from certain, the rights established in the abortion decisions would not appear to be violated by a prohibition on research that includes implantation of a blastocyst. Roe v. Wade establishes a woman's right to decide free of unwarranted governmental interference whether to terminate a pregnancy. In essence, the decision gives a woman absolute discretion to abort during the first two trimesters. It seems clear that it would be impermissible for a state to inquire into the motivation for such an abortion. But this is not to say that the Constitution similarly precludes restrictions on the initiation of certain types of pregnancies simply because a woman might have an unfettered right to terminate the pregnancy once conception has occurred.

C. Constitutional Issues Regarding A Refusal To Fund Or A Prohibition Against Research Involving Implantation With The Hope Of Childbirth.

Somewhat different considerations are applicable in IVF research procedures in which there is a hope that a child will be born. As in the other IVF research situations, it would not appear that any constitutionally protected fundamental interest in participating in research qua research could be asserted. However, where childbirth is hoped for, the arguably fundamental interests identified in Section II regarding procreation, bearing or begetting children, and marital privacy, would in all likelihood come into play.

As previously discussed, at least in certain circumstances there may be a constitutionally protected fundamental right to use IVF procedures to conceive and bear children. The reasons in favor of identifying such a fundamental right arguably have only an attenuated force, however, if, because of the experimental nature of the procedure, or for other reasons, the likelihood of success in producing a child is not great.<sup>105/</sup>

The presence of a significant risk that a child would be naturally aborted, or that a child might be damaged as a result of IVF conception or implantation, or that the mother may be injured as a result of the IVF research procedure, would also suggest that there may be a comparatively

strong governmental interest in restricting such experimental procedures on safety grounds. Moreover, the government might advance an interest in preserving the dignity of potential human life that applies more strongly in the case of restricting experimental IVF procedures even if it is intended for those procedures to produce a child. Whether such interests might be considered sufficiently compelling to justify a complete prohibition against use of experimental IVF procedures (or certain of them) could only be determined after an appraisal of precisely how risky and "experimental" the procedure might be, and the kind of manipulation that it might involve. <sup>106/</sup>

D. Additional Regulatory Considerations.

1. Safety Restrictions And Restrictions  
To Protect The Dignity Of Potential  
Human Life.

Rather than seeking to prohibit all IVF research that involves the formation, manipulation, and destruction of blastocysts, the government might seek to impose restrictions that merely control the conditions under which IVF research may be carried out. Similarly, HEW might wish to condition its funding of IVF research on adherence to some such restrictions.

It is quite likely, for example, that a state (or HEW) may seek to impose safety standards in connection with the IVF research it permits (or funds), or to impose standards



to protect the dignity of potential human life. Such restrictions will in all likelihood be sustained against constitutional attack if they are reasonable, and if they do not infringe on any constitutionally protected fundamental rights to pursue IVF research. Accordingly, reasonable safety regulations, or regulations to protect the dignity of potential human life, that place conditions on research funded by HEW, such as the conditions encompassed in the existing HEW regulations regarding fetal research, are not likely to be susceptible to successful constitutional challenge.<sup>107/</sup>

2. Regulation Of The Attending Physician's  
Role In Implantation And Abortion Decisions.

Section II discussed in the context of IVF for childbearing the advisability and constitutionality of regulatory provisions assigning to the physician the authority to decide whether a blastocyst should be implanted and whether an abortion should be performed. Similar concerns may arise in the research context.

In the case of research where there is a hope for birth, the policy and constitutional issues appear to be similar to those already discussed in Section II. Differences arise in the case of research where birth is not intended. In that case, disputes between the researcher and

the research participants regarding the desirability of implantation or abortion may be unlikely. Ordinarily it will be agreed in advance among the parties that the researcher should be in charge of such decisions, and the participants will have no special stake in the researcher's decision. Nevertheless, it seems clear that even if the researcher did not propose an abortion, a woman participating in IVF implantation research could not constitutionally be precluded from deciding to abort. It seems equally clear that the researcher could not constitutionally be empowered by law to compel an unwilling participant to abort. On the other hand, although it is not certain, it seems likely that the decision not to implant could constitutionally be entrusted solely to the researcher in the IVF research context, even in the absence of a compelling governmental justification. In the context of such research, the participants appear to have no fundamental procreative, bear or beget, or family privacy interest in implantation.

3. Regulations Requiring Consent Of Donors Or Research Participants.

State restrictions on IVF research, and HEW regulations regarding IVF research funded by HEW, may require that researchers secure the consent of donors of reproductive materials before using such materials in research. Such restrictions could clearly be sustained against constitutional challenge.

#### IV. Tort Liability For Injuries Arising From In Vitro Fertilization Procedures.

The purpose of this Section is to discuss the nature and extent of the federal government's potential liability in tort suits for damages that might arise in the course of IVF research or health care programs conducted by HEW, funded by HEW grants or contracts, or subject to Medicaid reimbursement.<sup>108/</sup>

Many actions, ranging from promulgation of regulations regarding IVF programs to treatment of an individual patient or subject by a physician or researcher, potentially could give rise to tort litigation against the United States. The actual risk to the government of such litigation will depend on the resolution of two threshold questions. The first is whether suit is barred by the doctrine of sovereign immunity -- a jurisdictional issue to be resolved under federal statutes and federal case law.<sup>109/</sup> The second is whether, assuming suit is not so barred, there is presented a substantive cause of action valid under state law.<sup>110/</sup>

##### A. Sovereign Immunity.

Under the doctrine of sovereign immunity, the United States may not be sued without its consent.<sup>111/</sup> The Federal Tort Claims Act (FTCA),<sup>112/</sup> provides such consent in some but not all tort suits. Under the FTCA, the United

States is liable for the "negligent or wrongful" acts or omissions of its "employees" acting within the scope of their office or employment "in the same manner and to the same extent" as a private individual would be under the law of the place where the tort occurs.<sup>113/</sup> As construed by the Supreme Court, the FTCA permits suits based on the negligent or intentionally wrongful conduct of government employees but does not authorize suits based on a theory of strict or absolute liability.<sup>114/</sup> In addition, the FTCA contains a number of exemptions from the Act's general waiver of sovereign immunity. The exemptions that appear most relevant to cases likely to arise from IVF programs include suits based on the performance of discretionary functions or duties and claims arising from certain specified torts including assault, battery, misrepresentation, and interference with contract rights.<sup>115/</sup> Thus, in order to avoid the bar of immunity a suit brought under the FTCA must be based on negligence or "some form of 'misfeasance or non-feasance'"<sup>116/</sup> by a government employee, but cannot be based on a discretionary function or on an action falling within the other specified exceptions.

What follows is an analysis of the principal provisions of the FTCA as they would probably be applied in the context of IVF.



1. The Requirement That The Tortfeasor Be An "Employee" Of The Federal Government.

Under the FTCA, the government is liable only for the negligence of its "employees."<sup>117/</sup> The FTCA defines the term "employee" to include officers or employees of federal agencies.<sup>118/</sup> Federal agencies in turn include

the executive departments, the military departments, independent establishments of the United States, and corporations primarily acting as instrumentalities or agencies of the United States but [do] not include any contractor with the United States. 28 U.S.C. § 2671.

Obviously, HEW is a federal agency, and its employees, ranging from the Secretary to administrators, physicians, and researchers, thus meet the initial definitional requirement of the FTCA.

In contrast, administrators, physicians, or researchers employed by state, local, or private hospitals or research institutions that may receive HEW grants or contracts for IVF programs would probably not be considered "employees" of the federal government for FTCA purposes. However, to the extent that HEW might control the day-to-day operations of an IVF program grantee or contractor by regulation or otherwise, a court might find a sufficient "employment" nexus between the federal government and the grantee or contractor to justify holding the federal government responsible for the negligent operation of the program.<sup>119/</sup>

Finally, it appears that the federal government would not be held to have consented to suits based on the negligence of physicians who may provide IVF services reimbursable by Medicaid. The federal government is even less involved with the day-to-day provision of services reimbursed by Medicaid than it is with the daily operation of grant or 120/ contract programs.

2. The "Discretionary Function" Exception  
To The Federal Tort Claims Act.

It remains to be seen whether suits based on negligent decisions or actions by HEW officers or employees would be barred by the discretionary function exception. Under the FTCA, sovereign immunity is not waived and, therefore, the government may not be liable, if the acts or omissions on which a claim is based are within the "discretionary function or duty" of a federal agency or federal 121/ employee.

The Supreme Court has given a broad interpretation to the discretionary function exception to the FTCA. In Dalehite v. United States, 346 U.S. 15 (1953), plaintiffs sought to recover against the United States for a death resulting from the explosion of fertilizer stored for use in a federal foreign aid program. The decision to manufacture the fertilizer had been made at the Cabinet level, and the

official appointed to administer the program had adopted a plan that contained particular manufacturing specifications. <sup>122/</sup>

The Court held that the discretionary function exception barred a suit alleging negligence in the decision to initiate the fertilizer program as a whole and the decision to embark upon the program without undertaking further experimentation regarding the fertilizer's explosiveness. The Court also found that the specific acts of negligence charged in the manufacture of the fertilizer -- all of which acts were performed pursuant to the administrative specifications -- fell within the discretionary function exception.

The Court explained its rationale as follows:

It is unnecessary to define, apart from this case, precisely where discretion ends. It is enough to hold, as we do, that the "discretionary function or duty" that cannot form a basis for suit under the Tort Claims Act includes more than the initiation of programs and activities. It also includes determinations made by executives or administrators in establishing plans, specifications or schedules of operations. Where there is room for policy judgment and decision there is discretion. <sup>123/</sup>

In concluding that the government's formulation of manufacturing specifications was entitled to immunity from suit, the Court focused on the fact that this activity involved the exercise of expert judgment, occurred "at a planning

rather than operational level," and "involved considerations <sup>124/</sup> more or less important to the practicability" of the program.

As one court has observed, if the Dalehite opinion were taken literally it could be interpreted to immunize a very wide range of decisionmaking:

The description of a discretionary function in Dalehite permits the interpretation that any federal official vested with decision-making power is thereby invested with sufficient discretion for the government to withstand suit when those decisions go awry. Most conscious acts of any person whether he works for the government or not, involve choice. Unless government officials (at no matter what echelon) make their choices by flipping coins, their acts involve discretion in making decisions. <sup>125/</sup>

Subsequent cases have not, however, construed Dalehite this <sup>126/</sup> broadly.

While some federal courts have focused on Dalehite's "planning-operational" distinction to answer whether Section 2680(a) bars suit, <sup>127/</sup> the trend appears to be for courts to analyze whether particular decisions of government employees are of the nature and quality Congress intended to put beyond judicial review by means of tort suit -- i.e., whether the <sup>128/</sup> decisions involve the formulation of basic government policy. As one court explained:



The discretionary acts sought to be exonerated by § 2680(a) must be conduct that brings to bear policy judgments, the balancing of a risk-benefit formulae. It is in those problem areas where the public imposes upon its decision makers both a duty and an unrestrained liberty to consider and construct a solution, that the results of such deliberations should be protected. Otherwise the threat of future litigation might intimidate the creativity of those decision makers burdened with the duty of working out a problem. <sup>129/</sup>

In accordance with this approach, courts have held that the Section 2680(a) exemption applies to: (1) the decision of HEW officials not to issue guidelines for sterilizations performed by OEO grantees; <sup>130/</sup> (2) the decision of the Pesticides Regulation Division of the Department of Agriculture that the labeling of a mercury fungicide met the safety requirements of the applicable statute; <sup>131/</sup> and (3) the decision of the Food and Drug Administration, pursuant to the statutory requirement for FDA approval of new drug applications, that "DES" was "safe for use." <sup>132/</sup>

On the other hand, judgments requiring "professional expert evaluation" do not qualify for the Section 2680(a) exemption on that ground alone. <sup>133/</sup> While the case law is not uniform, in many cases based on actions and decisions made by government physicians in the course of providing medical or psychiatric services, the federal government has been found to be amenable to suit. <sup>134/</sup> Liability in these cases

rests on the principle enunciated in Indian Towing Co. v. United States, 350 U.S. 61, 69 (1955), that although the government need not undertake a particular function, once it does, it must exercise due care in its implementation.<sup>135/</sup>

Finally, courts have held that the discretionary function exception will not bar suit where allegedly negligent conduct violates an administrative regulation<sup>136/</sup> intended to protect the plaintiff.<sup>137/</sup> Griffin v. United States, 500 F.2d 1059 (3d Cir. 1974), is illustrative. There the court found that the decision of the Food and Drug Administration's Division of Biologic Standards to release a production lot of polio vaccine did not fall within the discretionary function exception because the Division's decision was made in violation of HEW's own regulations.<sup>138/</sup>

Applying the principles set forth above to the IVF context, it would appear that a plaintiff would have little likelihood of success in a suit that alleged that the Secretary of HEW was negligent in his decision to conduct, fund, or provide Medicaid reimbursement for IVF research or health care programs or in his promulgation of regulations governing such programs.<sup>139/</sup> A plaintiff's chances of success in avoiding the bar of sovereign immunity would, however, be better if his suit were based on the negligence of subordinate HEW officers or employees who had designed or operated a particular IVF research or health care program in, for example, the National

Institutes of Health or a Public Health Service hospital. If the allegedly negligent conduct of the HEW administrators, physicians, or researchers constitutes a violation of HEW regulations, a plaintiff would have the greatest probability of success.<sup>140/</sup>

If, on the other hand, the alleged negligence did not violate departmental regulations, the result would be more problematical. Were it to be asserted that a particular program was negligently formulated (for example, if a research protocol included a practice or procedure that turned out to be unsafe and resulted in injury), a court might, citing Dalehite, find the specific plans to be "planning level" decisions involving judgments as to the "practicability" of the program.<sup>141/</sup> Another court, however, might conclude that the decision involved was more scientific than legislative, did not constitute the formulation of basic government policy, and simply was not the sort of decision that Congress intended to protect.<sup>142/</sup>

If a claim were advanced that an individual had been injured through the negligent operation of a particular program, the discretionary function exception would not likely bar suit. The decisions made by researchers or physicians in the course of treating individual subjects or patients would probably be held to fall outside the scope of the discretionary function exemption because these decisions resemble those ordinarily made by physicians in the

course of medical practice, tend to involve professional judgment or discretion rather than the setting of government policy, and reflect the government's obligation to exercise due care in performing the functions it has chosen to undertake.<sup>143/</sup>

3. Other Exceptions To The Federal Tort Claims Act.

Even if a suit were not barred by the discretionary function exception, it could not succeed if it fell within one of the exceptions listed in Section 2680(h) of the FTCA. These exceptions, however, would not likely provide immunity in most tort cases involving the treatment of research subjects or patients participating in IVF programs conducted by HEW employees.<sup>144/</sup>

One exception listed in Section 2680(h) is for claims arising from battery. While some forms of medical malpractice may technically constitute that tort,<sup>145/</sup> Section 233(e) of the Public Health Service Act, 42 U.S.C. § 233(e), provides that the FTCA's battery exception does not apply to the negligent performance of medical or surgical procedures or clinical studies or investigations performed by Public Health Service employees, including physicians and researchers. Thus, under this section, malpractice cases presumably could be brought against the government for injuries occurring in HEW-run IVF programs.<sup>146/</sup>



The FTCA's misrepresentation exception has been construed to prevent suits based on either negligent or willful misrepresentations.<sup>147/</sup> Yet even though medical malpractice cases may appear to rely in whole or in part on misrepresentations, they tend not to be barred by this exception.<sup>148/</sup> For example, courts have permitted suits involving the failure to warn a patient of medical risks and the failure to provide correct diagnostic information.<sup>149/</sup> In cases such as these, the gravamen of the action is the negligent performance of a duty owed to the plaintiff and the misrepresentation, if any, constitutes only a part of the negligence.<sup>150/</sup> It is, therefore, likely that similar suits involving IVF would be found to be beyond the reach of the Section 2680(h) exception.

#### 4. Personal Tort Liability Of HEW Officers And Employees.

While the foregoing discussion has focused on the potential tort liability of the government, a plaintiff may attempt to hold HEW officers or employees personally liable for tortious acts committed in connection with IVF programs. Their personal liability, however, does not appear to be substantial.

Administrators, researchers, and physicians employed by the Public Health Service are protected from liability by the Public Health Service Act which provides in relevant part that:

The remedy against the United States provided by [the FTCA] shall be exclusive of any other civil action or proceeding by reason of the same subject-matter against the [Public Health Service] officer or employee (or his estate) whose act or omission gave rise to the claim. 42 U.S.C. § 233(a).

This section appears to afford protection from personal liability if the FTCA permits suit to be brought against the United States.<sup>151/</sup> Public Health Service employees, therefore, remain amenable to suit only in the very few IVF-related situations in which Section 2680(h) would preclude suit against the government.<sup>152/</sup>

Moreover, there appears to be little risk of personal liability of those HEW administrators, including the Secretary, who are not employed by the Public Health Service but are involved with IVF programs.<sup>153/</sup> A successful suit against the United States would bar claimants from suing these officers,<sup>154/</sup> and the government in all likelihood could not seek indemnity from them.<sup>155/</sup> In the absence of recovery against the government, high-level HEW officials would probably not be subject to liability since, for reasons similar to those behind the discretionary function exception of the FTCA, they would likely be found immune from suit.<sup>156/</sup>

B. Possible Substantive Causes Of Action.

Assuming that the FTCA would permit certain IVF-related tort suits against the government based on the negligence of HEW administrators, physicians, or researchers, a complaint would additionally have to state a valid cause of action under the law of the state where the tort occurred.<sup>157/</sup> Some of the suits that might arise in the context of IVF fall within the commonly understood framework of ordinary medical malpractice or other negligence claims.<sup>158/</sup> It does not appear necessary to address them here. Other suits may allege causes of action in areas of tort law in which the parameters of liability have not yet been clearly defined. It is to these actions that the Memorandum now turns.

1. Actions On Behalf Of The Child.

Under some circumstances, suits might be brought on behalf of a child conceived through IVF to recover for an injury that occurred prior to implantation or during gestation.<sup>159/</sup> The general rule is that an action may be brought on behalf of a child for the consequences of prenatal injuries only if the child is born alive.<sup>160/</sup> Traditionally, live birth occurs when a fetus has left its mother's body and exhibits life signs such as independent breathing, arm or leg movement, or a beating heart.<sup>161/</sup>

There is some question whether recovery by a fetus who has been born alive would extend to pre-natal injuries sustained before it became "viable."<sup>162/</sup> While recovery has been limited traditionally to post-viability injuries, the trend has been for courts to permit suits for injuries sustained any time after conception.<sup>163/</sup> Indeed, at least one court has allowed a plaintiff to recover where the tortious conduct occurred several years before conception.<sup>164/</sup> Thus, while no suit for prenatal injuries involving IVF has yet been brought, there is some legal basis for a court to permit recovery for injuries inflicted on a blastocyst prior to or during implantation, provided, of course, that the fetus developing from the blastocyst is born alive.

In contrast to suits for pre-natal injuries, "wrongful life" actions might be brought seeking damages for birth itself rather than for injuries inflicted before birth. In these cases the allegation made on behalf of the child is in effect that he should not have been born at all. In the context of IVF, a "wrongful life" action might arise if a physician negligently advised or directed the selection of defective ova or semen or the implantation of a defective blastocyst.<sup>165/</sup>



Wrongful life suits have generally not been recognized by state courts.<sup>166/</sup> However, one appellate court (albeit not the highest court of the state) recently upheld a wrongful life cause of action brought on behalf of a child born with a fatal hereditary kidney disease.<sup>167/</sup> In that case, the parents' first child had died of the disease, and they sought medical advice regarding the likelihood that a future child would be afflicted. The defendant doctors inaccurately advised the parents that the chances of recurrence of the disease were negligible. Relying on the advice, the parents had a second child, who died at two and one half years of age. The court permitted the child's claim for damages.

## 2. Actions To Redress Injury To The Parents.

The parents of an IVF child might seek damages for economic loss and for physical and emotional suffering arising from IVF procedures. One possible kind of suit would be for injuries arising from destruction of the blastocyst against the parents' wishes. In Del Zio v. Presbyterian Hospital, 1974 Civ. 3588 (S.D.N.Y. 1978), prospective parents sought to recover for their pain and suffering caused by the deliberate destruction of an unimplanted blastocyst by a member of the hospital staff. The jury returned a \$50,000 verdict in favor of the plaintiffs.<sup>168/</sup>

Parents might also bring "wrongful death" actions to recover for losses suffered by them as a result of the

death of their child.<sup>169/</sup> While all states permit actions for wrongful death caused by pre-natal injuries where the death occurs after a live birth, many also allow recovery for the wrongful death of a viable fetus that is not born alive.<sup>170/</sup> It would be a substantial leap, but it is not inconceivable, that a wrongful death cause of action could be extended beyond its present reach to permit recovery for wrongful destruction of an unimplanted blastocyst. Indeed, the recovery in Del Zio, while under a different legal theory, seems to have served the same purpose as would such a wrongful death remedy.

Finally, parents may seek to recover in an action for "wrongful birth." Such suits might arise in the context of IVF under circumstances similar to those discussed regarding wrongful life suits -- where a deformed or abnormal child is born as a result of negligent medical advice or decision to proceed with IVF.

A number of courts have recognized that the birth of a child can, under some circumstances, give rise to a cause of action by the parents for economic loss and/or emotional distress.<sup>171/</sup> Such cases have been brought, for example, by parents of a child born after the failure of a sterilization operation<sup>172/</sup> or after the negligent filling of a prescription for birth control pills.<sup>173/</sup> In Park

v. Chessin, 60 App. Div.2d 80, 400 N.Y.S.2d 110 (1978), in addition to the wrongful life claim of the child, the parents were permitted to pursue a cause of action to recover the cost of medical care and support required during the child's short lifetime. Whether parents can recover damages for emotional distress is more problematical. In Howard v. Lecher, 53 App. Div.2d 420, 386 N.Y.S.2d 460 (1976), the parents of a child with a fatal genetic disease sued the obstetrician for negligence in failing to discover that the parents were carriers of the disease. The child died approximately two years after her birth, and the parents sought damages for the cost of her hospital, nursing, and funeral expenses and for their emotional distress. The Court recognized the legitimacy of the cause of action except for the awarding of damages for emotional stress.

\* \* \* \*

In sum, sovereign immunity does not protect the government from facing substantial tort liability in suits that may arise in the context of IVF-related programs conducted by HEW, and there is a substantial chance that at least some causes of action that may be brought are valid under state law.

Conclusion

This Memorandum has attempted to identify and explore the significant legal questions that would be raised by an HEW determination to support or to refrain from supporting IVF research or the use of IVF for procreative ends. The Memorandum has summarized the status of existing federal and state law regarding IVF; it has assessed whether and to what extent the use of IVF in both a research and procreative context may be constitutionally prohibited, restricted or regulated; and finally, it has outlined the nature and extent of the federal government's potential liability in tort suits for damages that might arise in the course of HEW sponsored IVF programs. We trust that the Memorandum will be of assistance to the Ethics Advisory Board and to others involved at this critical stage of the decisionmaking process.



## FOOTNOTES

\*/ The authors are practicing lawyers at Wilmer, Cutler & Pickering, Washington, D.C. The opinions expressed herein are those of the authors only and should in no way be attributed to their law firm.

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1/ As used in this Memorandum, the term "IVF" encompasses, in addition to the fertilization itself, donation of semen and extraction of ova, development of blastocysts in the laboratory, and implantation of a blastocyst in the uterus.

2/ See, e.g., 42 U.S.C. §§ 241-242o, 248-254b, 300a to 300a-7, 300b to 300b-5, 2001-2005f.

3/ See, e.g., 42 U.S.C. §§ 241-242o.

4/ See 42 U.S.C. §§ 1396 et seq.

In theory, funds for IVF services could also be available for Medicare recipients, but such a prospect appears unlikely in light of the language in Title XVIII of the Social Security Act, 42 U.S.C. §§ 1395 et seq., the nature of the covered population (i.e., persons over 65 and certain recipients of disability insurance under Title II of the Social Security Act), and the Medicare Bureau's traditional position that elective family planning procedures are not services covered under Title XVIII.

HEW might become involved with IVF in contexts additional to those already enumerated. The Food & Drug Administration, for example, might regulate the manufacture and use of drugs and devices employed in IVF procedures. And of course, the federal government's potential involvement in IVF-related matters extends beyond that of HEW. Military and Veterans Administration hospitals could provide IVF services. And the government might, through contracts entered into with insurance underwriters and other organizations, provide partial payment for IVF services for federal employees and their families. This Memorandum does not deal with these areas of potential government involvement in the IVF process, but the issues addressed may have some relevance to them.

5/ HEW's current appropriations statute provides that funds appropriated to HEW may not be used to perform abortions except in circumstances where carrying the fetus to term would endanger the life of the mother or result in "severe or long-lasting" damage to her physical health or where the mother is the victim of promptly reported rape or incest. Pub. L. No. 95-480, § 210, 92 Stat. 1567 (1978). On its face, this provision does not appear to preclude HEW involvement in IVF projects even if they entail the discarding of cultured, unimplanted blastocysts. Additionally, in enacting the statute Congress did not address the issues raised by IVF. Furthermore, the statute explicitly excludes from its prohibitions "drugs or devices to prevent implantation of the fertilized ovum. . . ." Pub. L. No. 95-480, § 210, 92 Stat. 1567 (1978). The statute would, however, appear to preclude the use of HEW funds for abortions (not otherwise meeting the statute's standards) involving blastocysts that were formed ex utero and subsequently implanted in a woman's uterus.

6/ The statutes that serve as authority for HEW to conduct, fund or reimburse IVF research or health care procedures are phrased in general terms such as "medical care," "family planning services," and "research . . . relating to physical . . . diseases and impairments of man. . . ." See statutes cited in notes 2-4 supra.

7/ These general provisions are codified in 45 C.F.R. §§ 46.101-46.122, 46.301. Note that the regulations in Part 46 of 45 C.F.R. do not cover any health care programs. HEW may wish to promulgate regulations regarding the provision of IVF health care services under HEW-conducted programs and/or to promulgate regulations specifying the circumstances under which IVF procedures are reimbursable under Medicaid.

8/ 43 Fed. Reg. 1759 (1978).

9/ 45 C.F.R. §§ 46.101-46.110.

10/ 39 Fed. Reg. 30648 (1974). The resulting fetal research regulations, adopted one year later, 40 Fed. Reg. 33528 (1975), are codified in 45 C.F.R. §§ 46.201-46.211, 46.301, subsequently amended in part, 40 Fed. Reg. 51638 (1975), 43 Fed. Reg. 1758 (1978).

11/ In addition to requiring review by the Ethics Advisory Board, the fetal research regulations set out the duties of Institutional Review Boards in connection with activities involving IVF. These duties also apply to research involving fetuses or pregnant women. 45 C.F.R. § 46.205.

12/ See 40 Fed. Reg. 33527 (1975); 39 Fed. Reg. 30650 (1974).

13/ 45 C.F.R. § 46.206(a)(1). See 45 C.F.R. § 46.201(a).

14/ Because in 1975 "biomedical research [was] not yet near the point of being able to maintain for a substantial period the non-implanted product of in vitro fertilization," 40 Fed. Reg. 33527 (1975), HEW saw no need at that time to address the matter of non-implanted fetuses in the fetal research regulations. The regulations do, however, apply to the product of IVF after it is implanted. See 45 C.F.R. § 46.203(b), (c).

One commentator has noted that the fetal research regulations define "pregnancy" as the period of time from confirmation of implantation until expulsion or extraction of the fetus, and has asked: ". . . by excluding from the definition of pregnancy the area between conception and implantation, has not the Commission and HEW legitimated in vitro fertilization by defining it as an area involving the nonhuman?" Horan, Fetal Experimentation and Federal Regulation, 22 Vill. L. Rev. 325, 327-28 (1977).

15/ For example, HEW regulations provide that nothing in the subpart pertaining to research involving fetuses, pregnant women and in vitro fertilization "shall be construed as indicating that compliance with the procedures set forth herein will in any way render inapplicable pertinent State or local laws bearing upon activities covered by this subpart." 45 C.F.R. § 46.201(b).

16/ Alaska Stat. § 20.20.010 (1975); Cal. Civil Code § 7005 (Deering Supp. 1978); Conn. Gen. Stat. § 45-69f to 69n (Supp. 1978); Fla. Stat. § 142.11 (Supp. 1978); Ga. Code §§ 74-101.1, 74-9904 (1973); Kan. Stat. § 23-128 to 129 (1974); La. Civ. Code Ann. art. 188 (West Supp. 1978); Md. [Estates and Trust] Code Ann. § 1-206 to 1-208 (1974); Md. Ann. Code art. 43, § 556E (Supp. 1978); Mont. Rev. Codes Ann. § 61-306 (Supp. 1977); N.Y. Dom. Rel. Law § 73 (McKinney 1974); N.C. Gen. Stat. § 49A-1 (1976); Okla. Stat. tit. 10, §§ 551-553 (Supp. 1977); Or. Rev. Stat. §§ 109.239, 109.243, 109.247, 677.355, 677.360, 677.365, 677.370, 677.990 (1977); Tenn. Code Ann. § 53-446 (Supp. 1977); Tex. Fam. Code Ann. tit. 2, § 12.03 (Vernon 1975); Va. Code § 64.1-7.1 (Cum. Supp. 1978); Wash. Rev. Code Ann. § 26.26.050 (Supp. 1977); Wyo. Stat. § 14-7-106 (1977). See also New York City Health Code Art. 21.



17/ See, e.g., Ariz. Rev. Stat. §§ 36-2301 to 36-2303 (Supp. 1977); Ill. Rev. Stat. ch. 38, §§ 81-21 to 81-35 (1977); Ind. Code §§ 35-1-58.1 to 35-1-58.5-6 (1976); Ky. Rev. Stat. Ann. § 436.026 (Baldwin 1977); La. Rev. Stat. Ann. 14, §§ 87-88 (West 1974 and Supp. 1978); Me. Rev. Stat. tit. 22, §§ 1591-1595 (1978); Mass. Ann. Laws ch. 112, §§ 12J-S (Michie/Law Co-op Cum. Supp. 1978); Minn. Stat. Ann. §§ 145.411-145.423 (West 1977); Mo. Rev. Stat. §§ 188.010-188.085 (Vernon Supp. 1978); Montana Criminal Code of 1973, Mont. Rev. Codes Ann. §§ 94-5-613 to 94-5-624 (Supp. 1977); Neb. Rev. Stat. §§ 28-4,143 to 28-4,164 (1975); N.D. Cent. Code §§ 14-02.1-01 to 14-02.1-12, 14-02.2-01 to 14-02.2-02 (Supp. 1977); Ohio Rev. Code Ann. §§ 2919.11-2919.14 (Page 1975); Pa. Stat. Ann. tit. 35, §§ 6601-6608 (Purdon 1977); S.D. Compiled Laws Ann. §§ 34-23A-1 to 34-23A-21 (1977); Utah Code Ann. §§ 76-7-301 to 76-7-314 (1953); Wyo. Stat. §§ 35-6-115 (1977). The Uniform Anatomical Gifts Act, adopted in pertinent part by forty-eight states and the District of Columbia, imposes consent requirements for research on dead fetuses and stillborn infants.

18/ A similar question arises regarding state homicide statutes. In most states, these laws apply only to fetuses that are born alive. In other states, however, such laws are said to apply at earlier points in the fetus' existence, and apparently in one jurisdiction they may apply from the moment of conception. Wilson, A Report on Legal Issues Involved in Research on the Fetus, published in National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, Research on the Fetus, HEW Pub. No. (os) 76-128, at 14-9. Whether ex utero blastocysts would be covered would be a matter for state judicial interpretation.

19/ For example, the Minnesota statute prohibits use of "a living human conceptus for any type of scientific . . . or other experimentation except to protect the life or health of the conceptus. . . ." Minn. Stat. § 145.422, subd. 1 (West 1977). A "human conceptus" is defined to include a "human organism, conceived either in the human body or produced in an artificial environment other than the human body," Minn. Stat. Ann. § 145.421 subd. 2 (West 1977). But the restriction applies only to a live conceptus, which must show "evidence of life, such as movement, heart or respiratory activity, [or] the presence of electroencephalographic or electrocardiographic activity." Minn. Stat. § 145.421 subd. 3 (West 1977).

20/ Uniform Anatomical Gifts Act § 1 (1968); Mass. Ann. Laws ch. 112, § 112J(a)IV (Michie/Law Co-op Cum. Supp. 1978); N.D. Cent. Code § 14-02.2-02 (Supp. 1977); Ohio Rev. Code Ann. § 2919.14 (Page 1975); S.D. Compiled Laws Ann. § 34-23A-17 (1977); Utah Code Ann. § 76-7-310 (1953).

21/ The statutes listed in note 17, supra (except for the Uniform Anatomical Gifts Act) appear in the context of restrictions on abortion. The focus of the Uniform Anatomical Gifts Act is on gifts after death by persons of all ages.



22/ In order to sharpen the constitutional analysis, it has been assumed in this Section that: (1) IVF techniques are sufficiently advanced so as to present no undue risk of defective childbirths or harm to prospective mothers undergoing the procedure and (2) all existing persons affected by the procedure have consented to its use.

It should also be noted at the outset that any constitutional analysis of governmental regulation of the procreative use of IVF is proceeding upon largely uncharted waters. Although analogies may be drawn to the development of privacy rights in cases that concerned "conception through intercourse," it is plain that such cases did not consider, and do not purport to define, analogous rights in the IVF context. Moreover, a review of the Supreme Court's privacy-related cases makes clear that constitutional analysis has often been shaped in unpredictable ways by evolving social attitudes and technological realities. Nonetheless, with these caveats in mind, the already decided privacy cases appear to present the most logical starting point for an analysis of the constitutional implications of IVF.

23/ See Whalen v. Roe, 429 U.S. 589, 603 n.30 (1977); Wynn v. Scott, 449 F. Supp. 1302, 1322 (N.D. Ill. 1978) ("Since these two [fetal experimentation] provisions do not infringe on a fundamental right, they are subject to a less demanding test of rationality. They are within the category of social and health matters which states are given broad latitude to regulate."), appeal dismissed for want of jurisdiction, 47 U.S.L.W. 3259 (Oct. 16, 1978), appeal pending in Seventh Circuit.

24/ Maher v. Roe, 432 U.S. 464, 478 (1977).

25/ Carey v. Population Serv. Intern'l, 431 U.S. 678, 686 (1977).

26/ Whalen v. Roe, supra, 429 U.S. at 599-600.

27/ Loving v. Virginia, 388 U.S. 1 (1967).

28/ Skinner v. Oklahoma, 316 U.S. 535 (1942).

29/ Eisenstadt v. Baird, 405 U.S. 438 (1972).

30/ Roe v. Wade, 410 U.S. 113 (1973).

31/ Prince v. Massachusetts, 321 U.S. 158 (1944).

32/ Pierce v. Society of Sisters, 268 U.S. 510 (1925).

33/ Carey v. Population Serv. Intern'l, supra, 431 U.S. at 687; Eisenstadt v. Baird, supra, 405 U.S. at 453.

34/ Skinner involved a challenge to a state habitual criminal sterilization law that mandated the compulsory sterilization of certain types, but not all, habitual criminals. In concluding that there was no compelling state

interest to justify such a statute, the court observed that an individual sterilized under the statute would be "forever deprived of a basic liberty." Skinner v. Oklahoma, supra, 316 U.S. at 541.

35/ See also Planned Parenthood v. Danforth, 428 U.S. 52 (1976) (at least five members of the Court expressly recognized that a man has a constitutional right to father and enjoy the association of his offspring. (Stewart and Powell, J.J., concurring; White and Rehnquist, J.J., and Burger, C.J., dissenting.)

36/ Indeed, in Carey, the Court itself suggested that it was principally concerned with state intrusion into the intimacy surrounding sexual intercourse:

[I]n a field that by definition concerns the most intimate of human activities and relationships, decisions whether to accomplish or to prevent conception are among the most private and sensitive. Carey v. Population Serv. Intern'l, supra, 431 U.S. at 685.

37/ The two basic assumptions set forth in note 22, supra, apply to each hypothetical -- i.e., that IVF is sufficiently advanced so as to present no undue risk of defective child-births or harm to prospective mothers undergoing the procedure and that all existing persons affected by the procedure have consented to its use.

38/ See Griswold v. Connecticut, 381 U.S. 479 (1965); Heymann and Barzelay, The Forest and the Trees: Roe v. Wade and its Critics, 53 B.U.L. Rev. 765, 771 (1973) ("Nonetheless it is apparent that, whatever the source, the right of a married couple to make its own decisions about contraception was clearly linked with the zone of protection from unwarranted Government intrusion into familial and procreative affairs established by . . . Pierce, Prince and Skinner.")

39/ IVF would not, of course, be the only medical method of escaping the procreative limitation of a marriage. Artificial insemination has long been available to couples as an alternative method of conception. But, as previously noted, despite the fact that artificial insemination is widely available, no court has yet considered whether there is a Skinner or other constitutional right to utilize the procedure.

40/ Eisenstadt v. Baird, supra, 405 U.S. at 453.

41/ No court has yet considered whether a married woman has a constitutional right to utilize artificial insemination.

42/ As in preceding hypotheticals, the claim of the couple would be even further weakened if the absence of genetic relationship was not dictated by necessity.

43/ Carey v. Population Serv. Intern'l, supra, 431 U.S. at 684-85.

44/ Skinner v. Oklahoma, supra, 316 U.S. at 541.

45/ Distinctions among the various ways that HEW may be involved in IVF, identified in the Introduction, are not relevant for purposes of the constitutional analysis in this Section and in Section III. Therefore HEW's involvement is variously referred to as "conduct," "funding" or "support."

46/ In a companion case, Poelker v. Doe, 432 U.S. 519, 521 (1977), the Court applied identical reasoning in rejecting a constitutional challenge to a policy of a city "to provide publicly financed hospital services for childbirth without providing corresponding services for non-therapeutic abortions."

47/ Maher v. Roe, supra, 432 U.S. at 474.

48/ Obviously, HEW and the states would not be free to limit access to IVF on grounds of race, religion, national origin, alienage, etc. The Memorandum assumes that the distinctions HEW and the states might draw in regulating access to IVF would not be based on suspect classifications such as these.

49/ An HEW restriction on funding of IVF might be viewed as a prohibition if:

(1) The restriction had the practical effect of foreclosing an individual from obtaining IVF through the use of his or her own funds. Thus, for example, an HEW regulation that banned the performance of IVF in all facilities that receive HEW funds might be deemed to have a sufficiently preclusive effect on an individual's ability to utilize the procedure as to be the equivalent of an outright prohibition.

(2) The regulation were to penalize an individual for utilizing IVF by imposing a forfeiture of benefits to which he would otherwise be entitled.

50/ U.S. Const. art. I, § 8.

51/ The Supreme Court has held that a limitation which would be rational, if imposed by a state, will similarly support the constitutionality of a federal enactment. See Steward Machine Co. v. Davis, 301 U.S. 548 (1937). Indeed, Congress has the authority to exercise its spending power to "provide for the . . . general Welfare." U.S. Const. art. I, § 8, cl. 1.

52/ A prohibition on the procreative use of IVF might also be founded on the judgment that IVF represents an immoral method of reproduction. A regulation founded on such a basis might be upheld if it were to be measured against the rational basis standard. Where fundamental rights are not



thereby infringed, the government has been afforded considerable latitude in enacting legislation that reflects moral values. See Maier v. Roe, 432 U.S. 464 (1977) (the government can refuse to fund non-therapeutic abortions in the first trimester); Doe v. Commonwealth, 403 F. Supp. 1199 (E.D. Va. 1975), aff'd 428 U.S. 901 (1976) (state can constitutionally penalize private consensual acts of sodomy). On the other hand, it seems unlikely that a court would deem the exercise of such a moral judgment as a compelling state interest. Implicit in a number of Supreme Court decisions is the judgment that moral considerations, standing alone, cannot justify an infringement of a fundamental freedom. See Roe v. Wade, 410 U.S. 113 (1973) (upholding women's rights to determine whether or not to abort); Carey v. Population Serv. Intern'l, 431 U.S. 678 (1977) (upholding individuals' rights to have access to contraceptives).

53/ 410 U.S. at 159.

54/ See, e.g., Krimmel & Foley, Abortion: Inspection into the Nature of Human Life and Potential Consequences of Legalizing its Destruction, 46 Cin. L. Rev. 725, 756-756 (1977):

Viewed from the perspective of an adult organism, the zygote represents the first time at which there is a specific form of life present, and a specific identity attributable to that life. As the zygote divides and grows, by the process of mitosis, this hereditary blueprint is exactly reproduced in every cell of the adult organism. Each of the offspring-cells contains as its governing part an exact replica of the genetic material of the zygote. Accordingly, at conception, for the first time, the zygote is a specific human being.

55/ Roe v. Wade, supra, 410 U.S. at 160.

56/ See, e.g., Heymann & Barzelay, The Forest and the Trees: Roe v. Wade and Its Critics, 53 B.U.L. Rev. 765, 776 (1973):

One cannot deny, and the Court did not deny, that some would attach great weight to the prospect of life from its earliest days when we have little more than a handful of cells possessing a rich genetic code. But much that we associate with the value of human life is not present at the earliest stages. There is no feeling nor thought of which we know. There is no reciprocal relationship to others that is reflected in need or love. There is no memory or fear. What most of us mean by life, what most of us care about when we think of protecting life, is not true of the 12 or 16



cells present on the third or fourth day after pregnancy nor is it present for some time thereafter. Indeed, so much has always been recognized by each of the 50 states in making abortion a lesser crime than homicide."

57/ It should be noted, however, that there are arguably significant differences between the factual situation presented to the Court in Roe v. Wade and that being discussed here. So long as IVF requires the formation of multiple blastocysts, the selection from among them of the "fittest" for implantation, and the destruction of the remainder, it is not inconceivable that a court might hold, notwithstanding Roe v. Wade, that the preservation of potential life and other life-related interests that the government might articulate are sufficiently strong so as to amount to a compelling state interest to prohibit IVF at least until such time as the procedure can be accomplished through the formation of a single blastocyst. Compare Wilson, Fetal Experimentation: Legal Implications of an Ethical Conundrum, 53 Den. L.J. 581, 606 (1976) ("even though Roe deems the fetus a nonperson for constitutional purposes, it may nevertheless be entitled to protection where the state demonstrates a compelling interest in the potentiality of life in the nonabortion context, or where the fundamental rights of the mother are not at issue").

58/ De Burgh v. De Burgh, 39 Cal.2d 858, 864-65, 250 P.2d 598, 601 (1952) (Traynor, J.).

59/ Weber v. Aetna Cas. & Sur. Co., 406 U.S. 164, 173 (1972).

60/ Compare Labine v. Vincent 401 U.S. 532 (1971) (upheld intestate law that barred illegitimates from sharing equally with legitimates in estate of their father) with Weber v. Aetna Cas. & Sur. Co., 406 U.S. 164 (1972) (declared state workman's compensation statute that denied equal recovery rights to dependent unacknowledged illegitimates unconstitutional because it did not foster the state's interest in promoting legitimate family relationships).

61/ See, e.g., Conn. Gen. Stat. § 45-69g (Supp. 1978); Okla. Stat. tit. 10, § 551 (Supp. 1977).

62/ Eisenstadt v. Baird, supra, 405 U.S. at 452.

63/ Indeed, the trend in modern adoption statutes has been to allow a single individual to adopt if the individual can demonstrate that he or she is able to care for and support the child. See, e.g., D.C. Code § 16-302.

64/ Kindregan, State Power Over Human Fertility and Individual Liberty. 23 Hastings L.J. 1401, 1413 (1972).

65/ None of the statutes cited at note 16, supra, controls the donor selection process.

66/ Oakley, Test Tube Babies: Proposals for Legal Regulation Of New Methods of Human Conception and PreNatal Development, 8 Family L. Quar. 385 (1974).

67/ See D. Dobbs, Remedies § 2.5 (1973).

68/ Indeed, states have traditionally exercised authority to prohibit socially unacceptable forms of employment. E.g., Montana Criminal Code of 1973, Mont. Rev. Codes Ann. §§ 94-5-602, 603 (Supp. 1977) (prohibition on prostitution). A number of states also prohibit individuals from engaging in the buying and selling of infants. E.g., 10 Pa. Cons. Stat. Ann. tit. 18 § 4305 (Purdon 1976); Colo. Rev. Stat. § 19-4-115 (1974).

69/ See note 22, supra.

70/ Roe v. Wade, 410 U.S. 113, 149 (1973).

71/ Cf. Reilly, In Vitro Fertilization - A Legal Perspective in Milunsky & Annas, Genetics And The Law, 359-375 (Plenum Press, 1976).

72/ The procedure for extracting ova, laparoscopy, has been described as "a routine part of investigations into infertility and other illnesses" that "does not damage tissue." Edwards & Steptoe, Biological Aspects of Embryo Transfer, in Law and Ethics of A.I.D. and Embryo Transfer at 16 (1973).

73/ There is a third variety of artificial insemination, called confused artificial insemination ("CAI"), in which the semen of the prospective father is mingled with that of a donor. This variety has been referred to as the "French firing squad technique" and has received no judicial or legislative treatment. See Wadlington, Artificial Insemination: The Dangers of a Poorly Kept Secret, 64 N.W.L. Rev. 777 782 n.20 (1970).

74/ Adoption of Anonymous, 74 Misc.2d 99, 345 N.Y.S.2d 430, 431 (Sur. Ct. 1973). See also Doornbos v. Doornbos, 23 U.S.L.W. 2308 (Sup. Ct. Cook County, Ill., Dec. 19, 1945). As one court recently noted, "dictum, at least, tells us that there would be no question that such husband-donor would be the father." C.M. v. C.C., 152 N.J. Super. 160, 377 A.2d 821, 824 (1977).

75/ See, e.g., Alaska Stat. § 20.20.010 (1975); Cal. Civil Code § 7005 (Deering Supp. 1978); Conn. Gen. Stat. § 45-69i (Supp. 1978); Fla. Stat. § 142.11 (Supp. 1978); Ga. Code § 74-101.1 (1973); Kan. Stat. § 23-128 (1974); La. Civ. Code Ann. Art. 188 (West Supp. 1978); Md. Est. & Trusts Code Ann. § 1-206b (1974); N.Y. Dom. Rel. Law § 73 (McKinney 1974); N.C. Gen. Stat. § 49A-1 (1976); Okla. Stat. tit. 10 § 552 (Supp. 1977); Or. Rev. Stat. § 109.243 (1977); Tenn. Code Ann. § 53-446 (Supp. 1977); Tex. Fam. Code (Supp. 1977); Va. Code § 64.1-7.1 (Cum. Supp. 1978); Wash. Rev. Code Ann. § 26.26.050 (Supp. 1977).

76/ See, e.g., Cal. Civil Code § 7005b (Deering Supp. 1978); Conn. Gen. Stat. § 45-69 (Supp. 1978); Or. Rev. Stat. § 109.239L (1977); Wash. Rev. Code Ann. § 26.26.050(2) (Supp. 1977).

77/ Kindregan, supra, 23 Hastings L.J. at 1410.

78/ As one commentator has observed:

To the extent that any consensus is appearing, the general rule seems to be that, in the absence of a conclusive presumption of legitimacy of a child born during wedlock, the AID child is illegitimate. It also seems, however, that judicial effort is made to encourage or enforce his support by a consenting husband/nonfather. Whether AID will be considered to be adultery in some circumstances is not as clear. Wadlington, supra, 64 N.W.L. Rev., at 785-86.

79/ See, e.g., Conn. Gen. Stat. § 45-691 (Supp. 1978); Kan Stat. § 23-128 (1974); Okla. Stat. tit. 10 § 551 (Supp. 1977).

80/ See, e.g., Smith, Through a Test Tube Darkly: Artificial Insemination and the Law, 67 Mich. L. Rev. 127, 144-45 (1968).

81/ In the development of AID common law, courts have generally been inclined to decide parental responsibility questions in accordance with principles of equitable estoppel. See, e.g., People v. Sorensen, 66 Cal. Rptr. 7, 437 P.2d 495 (1968); Gursky v. Gursky, 39 Misc. 2d 1083, 242 N.Y.S.2d 406 (Sup. Ct. 1963). That is, participants to a procedure have been made to bear the consequences voluntarily assumed by consenting to or participating in the procedure. In reliance upon a similar principle, a court might well conclude that the definitions of parental responsibilities spelled out by a contract should likewise be enforced.



82/ In Elrod v. Burns, 427 U.S. 347, 360-61 (1976), the Supreme Court held:

That is the notion that because there is no right to a government benefit, such as public employment, the benefit may be denied for any reason. Perry, however, emphasized that '[f]or at least a quarter-century, this Court has made clear that even though a person has no 'right' to a valuable governmental benefit and even though the government may deny him the benefit for any number of reasons, there are some reasons upon which the government may not rely. 408 U.S., at 597. Perry and Keyishian properly recognize one such impermissible reason: The denial of a public benefit may not be used by the government for the purpose of creating an incentive enabling it to achieve what it may not command directly.

83/ See, e.g., Conn. Gen. Stat. § 45-69h (Supp. 1978); Okla. Stat. tit. 10 § 553 (Supp. 1977); Or. Rev. Stat. § 677.365 (1977); Cal. Civil Code § 7005 (Deering Supp. 1978); Wash. Rev. Code Ann. § 26.26.050 (Supp. 1977).

84/ See generally Walters, Ethical Issues In Human In Vitro Fertilization And Research Involving Early Human Embryos, Report prepared for the Ethics Advisory Board (September 8, 1978).

85/ Given what we understand to be the current medical realities, we do not consider wholly ex utero IVF culminating in live birth.

86/ Report and Recommendations: Institutional Review Boards, 78 (1978) (footnote omitted).

87/ The National Commission's Report cited Robertson, The Scientists' Right to Research: A "Constitutional Analysis, U. So. Cal. L. Rev. \_\_\_\_ (in press). See also Delgado & Millen, God, Galileo, and Government: Toward Constitutional Protection for Scientific Inquiry, 53 Wash. L. Rev. 349 (1978).

88/ See Delgado & Millen, supra, at 372-79.



89/ Report and Recommendations: Institutional Review Boards, supra, at 79.

90/ See Robertson, supra, \_\_\_\_ U. So. Cal. L. Rev. at \_\_\_\_ (typescript pp. 77-78):

[A] key distinction must be made between [restrictions] aimed at the scientist's choice of and topic of research and [restrictions] indifferent to content that are concerned solely with the consequences of using certain research methods.

Professor Robertson takes the position that restrictions aimed at the kind of knowledge that a researcher seeks conflict with "the First Amendment's presumption against governmental restriction of the flow of information and ideas based on an assessment of the worth or utility of the ideas." Id. at \_\_\_\_ (typescript p. 78). But in his view restrictions against methods of research do not. Thus, he concludes that:

[L]aws restricting research with fetuses, children or incompetent persons promote non-content interests, the protection of the subjects' welfare, and would be valid, if narrowly drawn, despite a dampening effect on research with those populations. Id. at \_\_\_\_ (typescript p. 94).

91/ See generally Pell v. Procunier, 417 U.S. 817 (1974).

92/ See Delgado & Millen, supra, at 403 (indicating that governmental action may restrict "an individual scientist's right to carry out basic research . . . on grounds . . . legitimately falling within the state's funding or police power . . .").

93/ The newsgathering cases involve rights of access to information, not the right to perform experimentation to create information. See also United States v. O'Brien, 391 U.S. 367, 376 (1968) (if important or substantial governmental interests are furthered by prohibition against a certain kind of action, then the fact that prohibition works "incidental limitations on First Amendment freedoms" is not fatal to the prohibition).

The Supreme Court has indicated that: "The right to speak and publish does not carry with it the unrestrained right to gather information." Zemel v. Rusk, 381 U.S. 1, 16-17 (1965) (upholding a decision by the Department of State to deny a citizen a passport to Cuba). But see Robertson, supra, at \_\_\_\_\_ (typescript pp. 47-49) (stating that Kleindienst v. Mandel, 408 U.S. 753, 764-65 (1972), signals something of a retreat from the Zemel approach).

94/ Roe v. Wade, 410 U.S. 113, 153 (1973).

95/ See also Planned Parenthood v. Danforth, 428 U.S. 52, 71 (1976) (husband's disagreement regarding desirability of abortion cannot preclude wife's decision to abort since "it is the woman who physically bears the child and who is more directly and immediately affected by the pregnancy").

96/ Compare Stanley v. Georgia, 394 U.S. 557, 567 (1969) (state may not prohibit private possession of pornographic materials), with Paris Adult Theatre I v. Slaton, 413 U.S. 49, 57-69 (1973) (state may prohibit exhibiting obscene films because exhibition of such films affects public morality and not only the individual viewers).

The Supreme Court's decisions do not support a theory that an individual has a right to do anything he wants privately with his own body. See Doe v. Commonwealth, 403 F. Supp. 1199 (E.D. Va. 1975) (upholding constitutionality of statute prohibiting private acts of sodomy between adult consenting males), aff'd, 425 U.S. 901 (1976). See also Paris Adult Theatre I v. Slaton, 413 U.S., supra, at 68 n.15.

97/ On the other hand, as "experimentation" approaches "treatment" the constitutional issues become akin to those discussed in Section II of this Memorandum. For example, if IVF techniques were developed to the point of regular success in achieving childbirth, but it were necessary before implantation "experimentally" to culture the prospective parents' ova and semen in several media as a "dry run," a couple might argue that it has the same fundamental right to participate in that "dry run" as it has in participating in the ensuing implantation itself.

98/ Except, perhaps, in the situation alluded to in the preceding footnote, where "experimentation" approaches "treatment."

99/ In Roe v. Wade, concerns regarding the safety of a pregnant woman seeking an abortion were sufficient to justify state regulation of the procedures for abortion during the second trimester of pregnancy or later. But they were not compelling concerns and therefore would not justify a prohibition on abortion during the second trimester. 410 U.S. at 113, 163 (1973).

100/ Asserting such a position would not necessarily be inconsistent with permitting IVF for the purpose of bearing children. A court might regard as reasonable a governmental view that manipulation of (and perhaps even some necessary discarding of) blastocysts in the process of procreation is publicly acceptable because of a strong state interest in procreation, and yet determine that non-procreative manipulation (and destruction) is publicly unacceptable.

101/ There will be no procreation, no child will be born, and there will be no addition to the family.

102/ Cf. Katz v. United States, 389 U.S. 347 (1967).

103/ Cf. HEW Proposed Regulations on Research Involving Prisoners, 43 Fed. Reg. 1050, 1053 (1978) (prisoners prohibited from participating in research sponsored or conducted by HEW unless the research has the "reasonable probability of improving the health and well-being of the subject").

104/ Cf. Roe v. Wade, 410 U.S. 113, 162-63 (1973) (state interest in protecting potentiality of human life "grows in substantiality" as pregnancy approaches term).

105/ It is not at all certain, however, that the likelihood of success would be a dispositive factor in assessing an outright prohibition against such research. In many cases pregnancy through normal intercourse is unlikely, or the chances of successful gestation and delivery are slight or uncertain. Yet there seems little doubt that such attempts to produce a child would ordinarily be entitled to fundamental constitutional protection (at least in the marital context).

106/ For example, a very slight risk of damage to the IVF infant, as compared with the incidence of damage or defect in infants produced through ordinary conception, would be unlikely to establish a compelling governmental interest in prohibiting IVF procedures. On the other hand, if the chances of producing a defective child were extremely high, governmental prohibition of such procedures, even if intended to beget a child, might be justified so as to protect the potential child and to protect the state from having to bear the burden of maintaining such a defective child. See Buck v. Bell, 274 U.S. 200 (1927) (statute requiring sterilization of incompetents upheld as constitutional), cited with approval in Roe v. Wade, supra, 410 U.S. at 154.



107/ If, however, it were determined that there is a fundamental right to participate in particular IVF research, infringement on that right by restrictions intended to protect health or the dignity of potential human life is more problematic. The abortion cases suggest that reasonable regulations intended to protect these general interests may be sustained. But if they effectively prohibit the very acts that are constitutionally protected, then they may not withstand constitutional challenge unless supported by a compelling governmental interest. See generally Roe v. Wade, supra, 410 U.S. at 163; Planned Parenthood v. Danforth, supra, 428 U.S. at 75-79.

108/ The government could, of course, also be subject to suits for breach of contract in connection with HEW-conducted IVF programs. See 28 U.S.C. §§ 1346(a)(2), 1491.

109/ See, e.g., Laird v. Nelms, 406 U.S. 797, 799-800 (1972); Smith v. United States, 546 F.2d 872, 875-78 (10th Cir. 1976).

110/ See 28 U.S.C. § 1346(b).

111/ See, e.g., Feres v. United States, 340 U.S. 135 (1950).

112/ 28 U.S.C. §§ 1346(b), 2671-2680.

113/ 28 U.S.C. §§ 1346(b), 2674.

114/ Laird v. Nelms, supra.

115/ 28 U.S.C. § 2680(a), (h).

116/ Laird v. Nelms, supra, 406 U.S. at 800, quoting Dalehite v. United States, 346 U.S. 15, 45 (1953).

117/ 28 U.S.C. § 1346(b).

118/ 28 U.S.C. § 2671.

119/ In United States v. Orleans, 425 U.S. 807 (1976), the Supreme Court held that neither a community action agency operating as a non-profit corporation under state law and receiving funds from HEW's Office of Economic Opportunity, nor a neighborhood center operated by the community agency was a federal agency or instrumentality within the meaning of the FTCA. The Court found, therefore, that the center's employees were not federal employees for the purposes of that statute. In reaching that decision, the Court asserted that the key question was

not whether the community action agency receives federal money and must comply with federal standards and regulations, but whether its day-to-day operations are supervised by the Federal Government. Id. at 815 (Emphasis added).



The community action agency in issue received 80% of its support from OEO and had to comply with extensive OEO regulations and guidelines, concerning, for example, employment policies, accounting and inspection procedures, programmatic limitations, and application procedures. Nonetheless, the Court concluded that the federal regulations in effect in Orleans did not confer upon OEO the power "to supervise the daily operation" of the agency or of the neighborhood program. Id. at 818. Thus, the United States was immune from suit for the allegedly negligent supervision of an outing during which the respondent was injured.

120/ Under Medicaid, federal funds are given to participating states as reimbursement for state payments to providers of certain medical services to eligible recipients. The federal government does not supervise the day-to-day activities of participating physicians. The HEW Medicaid regulations do not directly govern the conduct of these physicians; they specify the circumstances under which financial participation may be available, 42 C.F.R. Part 405.

121/ 28 U.S.C. § 2680(a) provides in pertinent part that sovereign immunity is not waived for

any claim based upon . . . the exercise or performance or the failure to exercise or perform a discretionary function or duty on the part of a federal agency or an employee of the Government, whether or not the discretion involved be abused.

122/ These involved provisions regarding the type of chemical coating to be used on the fertilizer grains, the temperature at which the fertilizer was to be bagged, and the type of bagging and labelling to be employed. Dalehite v. United States, supra, 346 U.S. at 19-22, 38.

123/ Id. at 35-36.

124/ Id. at 42.

125/ Smith v. United States, 375 F.2d 243, 246 (5th Cir.), cert. denied, 389 U.S. 841 (1967).

126/ See, e.g., Rayonier, Inc. v. United States, 352 U.S. 315 (1957); Hatahley v. United States, 351 U.S. 173 (1956); Indian Towing Co. v. United States, 350 U.S. 61 (1955).

127/ See, e.g., United States v. Washington, 351 F.2d 913 (9th Cir. 1965); Mahler v. United States, 306 F.2d 713 (3d Cir.), cert. denied, 371 U.S. 923 (1962); United States v. Gregory, 300 F.2d 11 (10th Cir. 1962); Dahlstrom v. United States, 228 F.2d 819 (8th Cir. 1956); Eastern Air Lines, Inc. v. Union Trust Co., 221 F.2d 62 (D.C. Cir.), aff'd per curiam sub nom., United States v. Union Trust Co., 350 U.S. 907 (1955).

128/ See, e.g., Downs v. United States, 522 F.2d 997 (6th Cir. 1975); Griffin v. United States, 500 F.2d 1059 (3d Cir. 1974); Moyer v. Martin Marietta Corp., 481 F.2d 585 (5th Cir. 1973); Gray v. United States, 445 F. Supp. 337 (D. Tex. 1978); Relf v. United States, 433 F. Supp. 423 (D.D.C. 1977).

129/ Gray v. United States, supra, 445 F. Supp. at 340.

130/ Relf v. United States, supra, 433 F. Supp. at 423.

131/ First National Bank in Albuquerque v. United States, 552 F.2d 370 (10th Cir.), cert. denied, 434 U.S. 835 (1977).

132/ Gray v. United States, supra, 445 F. Supp. at 340.

133/ Hendry v. United States, 418 F.2d 774, 783 (2d Cir. 1969). See also J.H. Rutter Rex Mfg. Co. v. United States, 515 F.2d 97, 99 (5th Cir. 1975); Griffin v. United States, supra, 500 F.2d at 1066.

134/ See, e.g., Hendry v. United States, supra, 418 F.2d 774 (determination by Public Health Service psychiatrist and psychologist that ship's officer was unfit for sea duty held not within Section 2680(a) exemption); White v. United States, 317 F.2d 13 (4th Cir. 1963) (decision to allow freedom of movement to psychiatric patient held not within Section 2680(a) exemption); Fair v. United States, 234 F.2d 288 (5th Cir. 1956) (release of psychiatric patient held not within Section 2680(a) exemption); Costley v. United States, 181 F.2d 723 (5th Cir. 1950) (injection of harmful substance causing paralysis held not within Section 2680(a) exemption). But see, e.g., Blitz v. Boog, 328 F.2d 596 (2d Cir.), cert. denied, 379 U.S. 855 (1964) (illegal detention and improper treatment in psychiatric hospital held within Section 2680(a) exemption); Smart v. United States, 207 F.2d 841 (10th Cir. 1953) (unsupervised release of psychiatric patient held within Section 2680(a) exemption).

135/ See also Ingham v. Eastern Airlines, Inc., 373 F.2d 227, 236 (2d Cir. 1967).

136/ See, e.g., United Airlines, Inc. v. Wiener, 335 F.2d 379, 393-94 (9th Cir. 1964) (Air Force's designation of permissible flying areas, although an unreviewable discretionary decision had there been compliance with applicable regulations, held removed from Section 2680(a) exemption by failure to make prior study required by regulations); Donohue v. United States, 437 F. Supp. 836 (E.D. Mich. 1977) (suspension of HUD mortgage insurance license without full hearing held not barred by Section 2680(a) where suspension violated agency regulations).

137/ Cf. Clemente v. United States, 567 F.2d 1140 (1st Cir. 1977), cert. denied, \_\_\_ U.S. \_\_\_, 98 S.Ct. 1876 (1978); Griffin v. United States, supra, 500 F.2d at 1069-70.

138/ The regulation required the Division of Biologic Standards to find, by a comparative analysis of test results, that the neurovirulence of the test lot did not exceed that of a reference strain and enumerated five criteria as evidence of neurovirulence. DBS (and the court) construed the regulations as permitting it to weigh the criteria in accordance with the degree to which it believed each reflected neurovirulence. Because the decision to release the lot was predicated on a factor called biological variation, consideration of which was not authorized by the regulations, the court concluded that DBS's decision was not immunized from judicial review. The court reasoned that no discretion was conferred upon DBS to "disregard the mandatory regulatory command"; that by not using the criteria listed in the regulation DBS acted outside the scope of its authority; and that violating a non-discretionary command "[took] what otherwise might be characterized as a 'discretionary function' outside the scope of the statutory exception." Griffin v. United States, supra, 500 F.2d at 1069 (footnote omitted).

While the court's holding hinges on the violation of the regulation, there also is language to indicate that, even if the regulation had not been violated, the discretionary function exception would not have barred suit. The administrative decision at issue was "that of a professional measuring neurovirulence," and DBS's function "was limited to merely executing the policy judgments of the Surgeon General." Griffin v. United States, supra, 500 F.2d at 1066. The court stated:

Where the conduct of Government employees in implementing agency regulations requires only performance of scientific evaluation and not the formulation of policy, we do not believe that the conduct is immunized from judicial review as a 'discretionary function.' Ibid.

139/ See Dalehite v. United States, supra, 346 U.S. 15; Relf v. United States, supra, 433 F. Supp. 423.

Plaintiffs might argue that in light of the risks accompanying IVF procedures, the Secretary was negligent in permitting or supporting IVF programs or in promulgating pertinent regulations. Whether a particular kind of



government program is safe enough to be conducted is the sort of decision that the Dalehite Court explicitly, and without any difficulty, found to be immune. Dalehite v. United States, supra, 346 U.S. at 37-38. Similarly, where a regulation mandates particular procedures that, when followed result in injury, Dalehite seems to preclude suit. See, Dalehite v. United States, supra, 346 U.S. at 38-42.

Plaintiffs could argue that the conduct of IVF programs or the promulgation of regulations covering those programs, IVF grants and contracts, or Medicaid reimbursement fall outside HEW's statutory authority. If this were true, the discretionary function exception would not apply. Cf., Hatahley v. United States, 351 U.S. 173, 181 (1956). But especially in view of HEW's pervasive activities in similar areas, this argument seems far-fetched.

140/ See Griffin v. United States, supra, 500 F.2d. 1050.

141/ Dalehite v. United States, supra, 346 U.S. at 42. If the decision at issue involved evaluation of risks and benefits to the public and if it were made to fulfill the requirements of a regulation, immunity might also be found. Cf. First National Bank in Albuquerque v. United States, supra, 552 F.2d 370; Gray v. United States, supra, 445 F. Supp. 337. In these cases, however, the decisions were made by federal regulatory agencies acting as such -- a broader context than the implementation of a specific IVF program.

142/ Cf. Downs v. United States, supra, 522 F.2d at 997; Griffin v. United States, supra, 500 F.2d at 1064; Gray v. United States, supra, 445 F. Supp. at 340.

143/ See, e.g., Indian Towing Co. v. United States, supra, 350 U.S. at 69; Hendry v. United States, supra, 418 F.2d. 774.

144/ Those few IVF tort cases involving interference with contract rights of the parties, see, e.g., Del Zio v. Presbyterian Hospital, discussed infra, could conceivably be barred by Section 2680(h), although the tort of interference with contractual relations normally applies in commercial settings. See Hendry v. United States, supra, 418 F.2d at 779.

145/ See, e.g. Moos v. United States, 225 F.2d 705 (8th Cir. 1955) (suit for injury from operation on wrong leg held barred by Section 2680(h)); Lane v. United States, 225 F. Supp. 850 (E.D. Va. 1964) (operation of wrong knee technically constituted a battery but suit for a resulting injury held not barred by Section 2680(h)).



146/ An argument does remain that an intentional rather than negligent error would not be covered by Section 233(e) and would therefore be barred by Section 2680(h). The vast majority of malpractice cases, however, are likely to allege negligent rather than willful misconduct.

147/ See, e.g., United States v. Neustadt, 366 U.S. 696 (1961); Rey v. United States, 484 F.2d 45 (5th Cir. 1973).

148/ Rather, the misrepresentation exemption appears to have been intended to apply to the traditional tort of misrepresentation that would "arise most often in the course of business transactions." Ramirez v. United States, supra, 567 F.2d at 856, citing United States v. Neustadt, supra, 366 U.S. 696. See also Hall v. United States, 274 F.2d 69 (10th Cir. 1959).

149/ See, e.g., Ramirez v. United States, 567 F.2d 854 (9th Cir. 1977); Beech v. United States, 345 F.2d 872 (5th Cir. 1965); Betesh v. United States, 400 F. Supp. 238 (D.D.C. 1974). But see Matthews v. United States, 456 F.2d 395, 398 (5th Cir. 1972) (dicta).

150/ See, e.g., Hicks v. United States, 511 F.2d 407 (D.C. Cir. 1975); Beech v. United States, supra, 345 F.2d 872; United Airlines v. Wiener, supra, 335 F.2d 379; Betesh v. United States, supra, 400 F. Supp. 238.

151/ Section 233(a) may be read more broadly as limiting plaintiffs to the recovery, if any, permitted by the FTCA. This reading is consistent with the legislative purpose behind Section 233(a), which was to protect Public Health Service physicians from the expense of malpractice insurance. See 116 Cong. Rec. 42542-43 (Dec. 18, 1970). However, because this reading would leave injured parties without any remedy, a court might well adopt the narrower reading of Section 233(a) set out in the text.

152/ Where suit against the United States is barred by the Section 2680(a) discretionary function exception, the same rationale would likely prevent suit against the employee himself. See, e.g., Jackson v. Kelly, 557 F.2d 735 (10th Cir. 1977); Henderson v. Bluemink, 511 F.2d 399 (D.C. Cir. 1974).

153/ All HEW physicians or researchers involved with IVF can be expected to be employees of the Public Health Service. Their personal liability would be covered by the discussion in the previous paragraph of text.

154/ 28 U.S.C. § 2676.

155/ See United States v. Gilman, 347 U.S. 507 (1954).

156/ See, e.g., Doe v. McMillan, 412 U.S. 306, 319 (1973); Barr v. Matteo, 360 U.S. 564, 569 (1959); Spalding v. Vilas, 161 U.S. 483 (1896). Cf. Jackson v. Kelly, supra, 557 F.2d 735; Henderson v. Bluemink, supra, 511 F.2d 399.

157/ 28 U.S.C. §§ 1346(b), 2674. See, e.g., Simon v. United States, 438 F. Supp. 759 (S.D. Fla. 1977). Note that if a claim falls within one of the torts listed in Section 2680(h) of the FTCA, e.g. battery or misrepresentation, sovereign immunity is not waived and suit cannot be brought even though the cause of action is valid under state law.

158/ A woman might, for example, be injured during negligent extraction of ova or implantation of a blastocyst.

159/ It seems clear that there is no legal basis for a personal injury suit brought on behalf of a discarded blastocyst.

160/ See, e.g., Sox v. United States, 187 F. Supp. 465 (E.D.S.C. 1960); Woods v. Lancet, 303 N.Y. 349, 102 N.E.2d 691 (1951); Williams v. Marion Rapid Transit, 152 Ohio St. 114, 87 N.E.2d 334 (1949). See also, W. Prosser, The Law of Torts 336-37 (4th ed. 1971).

161/ See Towards a Practical Implementation of the Abortion Decision, 25 DePaul L. Rev. 676, 677, 695-96 (1976).

162/ "Viability" has been defined by the Supreme Court as the point at which the fetus is "potentially able to live outside the mother's womb, albeit with artificial aid." Roe v. Wade, supra, 410 U.S. at 160. Thus "viability" and "live birth" are not synonymous.

163/ See, e.g., Sylvia v. Gobeille, 101 R.I. 76, 220 A.2d 222 (1966) (viability standard rejected); Sinkler v. Kneale, 401 Pa. 267, 164 A.2d 93 (1960) (fetus one month old at time of injury). Hornbuckle v. Plantation Pipe Line Co., 212 Ga. 504, 93 S.E.2d 727 (1956) (fetus six weeks old at time of injury). See also Torts Prior to Conception: A New Theory of Liability, 56 Neb. L. Rev. 706, 709-10 (1977).

164/ Renslow v. Mennonite Hosp., 40 Ill. App. 3d 234, 351 N.E.2d 870 (1976) (upholding infant's suit for injuries sustained as a result of blood transfusion administered to mother eight years prior to infant's birth).

165/ Even if an action for wrongful life involved a claim based on misrepresentation, it would probably not be barred by the misrepresentation exemption of the FTCA.

166/ See, e.g., Gildiner v. Thomas Jefferson Univ. Hosp., 451 F. Supp. 692 (E.D. Pa. 1978); Stills v. Gratton, 55 C.A.3d 698, 127 Cal. Rptr. 652 (1976); Karlsons v. Guerinot, 57 App. Div.2d 73, 79-81, 394 N.Y.S.2d 933, 937 (1977); Williams v. State, 18 N.Y.2d 481, 276 N.Y.S.2d 885, 223 N.E.2d 343 (1966); Stewart v. Long Is. Coll. Hosp., 35 App. Div.2d 531, 313 N.Y.S.2d 502 (1970), aff'd, 30 N.Y.2d 695, 332 N.Y.S.2d 640, 283 N.E.2d 616 (1972); Gleitman v. Cosgrove, 49 N.J. 22, 227 A.2d 689 (1967); Zepeda v. Zepeda, 41 Ill. App.2d 240, 190 N.E.2d 849 (1963), cert. denied, 379 U.S. 945 (1964).

167/ Park v. Chessin, 60 App. Div.2d 80, 400 N.Y.S.2d 110 (1977).

168/ If Del Zio had involved an Hew-conducted program, and if suit had been brought against the United States, a court might possibly have found the suit barred by the "interference with contract rights" or "battery" exceptions to the FTCA. In a case involving negligent rather than intentional destruction of a blastocyst, however, the FTCA would not preclude the government's liability. See discussion at p. 32, supra.

169/ Note that any wrongful death action against the United States is subject to the damages limitation of the FTCA. See 28 U.S.C. § 2674.

170/ See, e.g., Simmons v. Howard Univ., 323 F. Supp. 529 (D.D.C. 1971); Eich v. Town of Gulf Shores, 293 Ala. 95, 300 So.2d 354 (1974). See also Simon v. United States, supra, 438 F. Supp. at 761; Roe v. Wade, supra, 410 U.S. at 162; Towards a Practical Implementation of the Abortion Decision, supra, 25 DePaul L. Rev. at 683; Prosser, supra, at §§ 55, 127.

171/ See, e.g., Gildiner v. Thomas Jefferson Univ. Hosp., supra, 451 F. Supp. 692; Park v. Chessin, supra, 400 N.Y.S.2d 110; Karlsons v. Guerinot, 394 N.Y.S.2d 933; Stills v. Gratton, supra, 127 Cal. Rptr. 652. But see, e.g., LaPoint v. Shirley, 409 F. Supp. 118 (W.D. Tex. 1976); Aronoff v. Snider, 292 So.2d 418 (Fla. 1974); Gleitman v. Cosgrove, supra, 227 A.2d 689.

172/ See, e.g., Custodio v. Bauer, 251 Cal. App.2d 303, 59 Cal. Rptr. 463 (1967).

173/ See, e.g., Troppe v. Scarf, 31 Mich. App. 240, 187 N.W.2d 511 (1971).





LEGAL IMPLICATIONS OF IN VITRO FERTILIZATION  
AND ITS REGULATION

Barbara F. Katz, J.D.



## I. Introduction

Recent events in England, which witnessed the birth of the world's first "test tube" baby, or baby conceived by means of in vitro fertilization (IVF), have elevated the serious medical, ethical, and legal issues surrounding this biomedical advance into the public forum.<sup>1</sup> Questions arise such as whether IVF is a non-human form of reproduction and is therefore immoral as a dehumanizing process; whether IVF is unethical and illegal experimentation with human beings; whether the state of science involved in IVF has not reached the point to warrant the participation of human beings; whether the potential danger of IVF children being born with physical abnormalities can be resolved; whether the law will create obstacles to the development of the process and/or to the individuals involved in it.

Resolution of most of the above problems is beyond the scope of the present paper. However, an examination of the role of the legal system in the IVF controversy will be undertaken. Based on the result of this analysis of the legal issues raised by IVF, the question of restriction of this type of research will be explored. Thus, a conclusion regarding the legal implications of IVF will form the basis for determining whether research in the area can be regulated, and if so, by what means.

## II. Background: The IVF Process

In order to understand the legal implications of IVF, it is first necessary to briefly summarize what the process itself involves, and the potential practical applications of that process.

The initial step in undertaking an IVF procedure is for the woman to be treated with hormones to stimulate maturation of eggs in the ovary. To locate the ovary, a laparoscope is inserted through an incision in the abdominal wall. Under direct vision, a needle is then inserted into the ovary to draw out several eggs. The eggs are placed in a dish containing blood serum and nutrients, to which sperm is added for fertilization. Once an egg is fertilized by one of the spermatozoa, it is then transferred to another dish of blood serum and sustaining nutrients. For the next three to six days, the fertilized egg divides, creating a cluster of cells called a blastocyst. After the woman receives further hormone treatment to prepare the uterine lining, the blastocyst is placed in the uterus, where it attaches to the wall and, hopefully, normal embryo development proceeds.<sup>2</sup>

There are still several outstanding medical problems facing the evolution of IVF into generally accepted ordinary medical practice. At the present time it is considered an experimental technique, without assurances that an IVF conceptus will survive to term or that IVF infants will not face a heightened risk of having birth defects.

Thus, for example, only a small fraction of the eggs removed from the woman are presently able to be fertilized and grow, due to the difficulty of finding a culture medium which imitates the environment of the mother's body.<sup>3</sup> In addition, implantation can only occur during a short portion of the menstrual cycle, so that the timing of the transplantation creates a significant problem.<sup>4</sup> Finally, it may be possible that the unavoidable manipulation of the eggs and the conceptus during the IVF procedure may lead to severe birth defects in IVF infants.<sup>5</sup>



Numerous scenarios for the practical application of the IVF process are feasible, each step becoming progressively more controversial. First is the use presently envisioned, with a woman who is infertile by virtue of blocked or missing Fallopian tubes achieving pregnancy by having one of her own eggs fertilized in the laboratory with her husband's sperm, and thereafter having the blastocyst implanted in her uterus.

Second, a woman capable of carrying a fetus to term but unable to produce normal egg cells will have the fertilized egg of another woman implanted in her uterus. There are several options here. In one variation, the egg is fertilized in vivo, in the uterus of the donor, via artificial insemination with the sperm of the recipient's husband, surgically removed from the donor's Fallopian tube at the appropriate moment, and then immediately implanted into the recipient's uterus. Another variation involves the in vitro fertilization of the donor's egg with the sperm of the recipient's husband, with subsequent implantation into the recipient's uterus.

Third, a woman with healthy tubes and ovaries, but with a condition that might be dangerously or even fatally aggravated by a pregnancy, has her egg, whether fertilized in vitro or in vivo, implanted into a second woman, who carries the fetus to term as a personal favor or in return for monetary compensation, after which she gives the baby back to its genetic mother.

Fourth, a woman who wants children, but for personal reasons, such as a desire not to disrupt career advancement, does not want to go through a pregnancy, arranges for a "surrogate mother" as described above.

Fifth, and certainly not within the foreseeable future, but a potential eventual application of the techniques involved nevertheless, women in general are able to select prepackaged embryos with clearly specified characteristics for implantation. This is not considered by all to be as far-fetched as it sounds. The late Dr. H. J. Muller, Nobel Prize winner in physiology and medicine, seriously advocated that prospective parents forgo egotistical desires to reproduce their own genetic characteristics and, instead, to help improve the human race by constructing their children from the "best" available egg and sperm cells. Dr. E. S. E. Hafez, an experimental biologist who has done animal research on embryo freezing, believes that there will come a time when parents will be able to select from one-day-old frozen embryos, guaranteed free of all genetic defects, with sex, eye-color, probable I.Q. and other traits described in detail on the label.<sup>6</sup>

### III. Family Law Ramifications of IVF

IVF raises few issues of family law that artificial insemination has not already raised.<sup>7</sup> Therefore, a review of the judicial and legislative treatment of family law issues arising from the use of artificial insemination will help illuminate the probable treatment by the law of similar issues in the IVF area.

There are two types of artificial insemination. Homologous insemination (AIH) involves the injection by instrument of the husband's sperm into the woman's reproductive tract to induce pregnancy. Alternatively, heterologous insemination (AID) involves semen from one or more donors.<sup>8</sup> In general, the legal response to issues raised by artificial insemination has been inconsistent, and even contradictory at times, thereby making prediction extremely difficult.

There are very few legal problems with AIH, since the resulting child is the biological offspring of both husband and wife. One question which has been raised is whether or not AIH constitutes consummation of the marriage for purposes of an annulment. The court in the English case L. v. L.<sup>9</sup> held that it did not and granted the wife's request for an annulment seven years after the couple had conceived a child through AIH.

Another unresolved issue concerns the legitimacy and inheritance rights of a child conceived and born after the husband's death through the use of frozen sperm. Most relevant statutes only apply the presumption of legitimacy to a child born within 300 days after dissolution of a marriage, either by death or divorce.<sup>10</sup> A third problem involves the potential of physician liability, which will be discussed in more detail below, as it is an issue which pervades this entire area.

On the other hand, AID presents a variety of legal problems. Early cases in the United States, England, and Canada held that the practice of AID was equivalent to adultery. Such a holding provides grounds for divorce as well as the basis for possible criminal prosecution.<sup>11</sup> The crucial issue involved is whether or not adultery requires a sexual act or whether it merely encompasses any action giving rise to the possibility of illegitimate conception.<sup>12</sup> This issue generally arises as a defense in a divorce or support action.<sup>13</sup>

An early Canadian case, dealing with a woman who had agreed to AID without her husband's consent, held in Orford v. Orford<sup>14</sup> that her action constituted adultery. The court's dictum provides the basis for many subsequent artificial insemination decisions.<sup>15</sup> It stated that the

essential element of adultery is not so much "the moral turpitude of the act of sexual intercourse" as it is "the possibility of introducing into the family of the husband a false strain of blood. Any act on the part of the wife which does that would, therefore, be adulterous."<sup>16</sup> Thus, this definition of adultery shifts the crucial point from the sexual act of penetration to any act which might introduce a false strain of blood into the family. However, a close reading of the opinion reveals judicial skepticism that there had been artificial insemination rather than normal sexual intercourse.<sup>17</sup>

The first American case on the subject of AID found that this procedure, even without the husband's consent, was not adultery.<sup>18</sup> However, the judge refused to accept the wife's statement that she had had no sexual contact with the father of the child. In addition, the case was not officially reported, and has not traditionally been followed. A later unreported Illinois lower court decision held that the use of AID constituted adultery even though the husband had consented.<sup>19</sup>

A modern trend may be discerned in cases such as MacLennan v. MacLennan.<sup>20</sup> This case considered the adultery question at length and presented a well-reasoned decision more in line with modern thinking. In an action for divorce brought by the husband on grounds of adultery, the wife claimed that her child was born as the result of AID, to which her husband had never consented. The court defined "adultery" as follows:

1. For adultery to be committed there must be the two parties physically present and engaging in the sexual act at the same time.
2. To constitute the sexual act there must be an act of union involving some degree of penetration of the female organ by the male organ.



3. It is not a necessary concomitant of adultery that male seed should be deposited in the female's ovum.
4. The placing of the male seed in the female ovum need not necessarily result from the sexual act, and if it does not, but is placed there by some other means there is no sexual intercourse.<sup>21</sup>

Under this definition of adultery, it seems unlikely that a present-day court would find that AID constituted adultery.

The only case dealing with the adultery issue to be heard by a state supreme court was People v. Sorenson. Although determination of the adultery problem was not of primary importance to the court's decision, it nevertheless stated that it would be "patently absurd" to hold that AID constituted adultery, since the physician performing the act could be a woman or the husband might even inject the semen himself. The court also rejected the notion that adultery could be committed with the donor of the semen since, at the time of the injection, the donor could be far away physically or even dead.

A related crucial question is the status of the child conceived as the result of AID. In those cases in which AID was held an adulterous act, the resulting child was found to be illegitimate. The question of illegitimacy has also arisen apart from any discussion of adultery. Indeed, many courts have held that a child born by AID is illegitimate without giving any regard to whether or not the husband gave his consent.

As a practical matter, however, it is difficult to prove that an AID child is illegitimate. First is the fact that most states have a statute providing a rebuttable presumption that a child born within a marriage is the legitimate issue of that marriage. Such a presumption can be rebutted only by clear and convincing evidence that the husband

is not the father. Barring complete sterility or impotency of the husband such a presumption is difficult to rebut. Many physicians will mix the semen of the husband and the donor and, in addition, physicians will often select donors who have the same bloodtype and similar physical characteristics as the husband so as to prevent bastardization by blood tests.

A series of cases on the question of legitimacy began in 1948 with a New York lower court decision, Strnad v. Strnad.<sup>22</sup> This involved a custody battle between the wife and her former husband, who had consented to the artificial insemination of his wife. The court held that the husband's parental rights concerning his AID children were akin to those of an adopting foster father, so that the children were legitimate.<sup>23</sup>

The next New York case concerned a habeas corpus proceeding in which the father sought a continuation of custody and visitation rights granted him under a separation agreement with his former wife.<sup>24</sup> Upon the woman's remarriage she refused to permit her ex-husband to see the children. When he filed the habeas corpus action, for the first time she alleged that the children were conceived by artificial insemination. The court found that the stipulations of the original separation agreement estopped the mother from raising the matter of AID because of potential detriment to the children.<sup>25</sup>

The case of Gursky v. Gursky<sup>26</sup> involved the situation in which the husband and wife had consented to the administration of AID and the wife later sued for divorce, asking for support for the resulting child. The court ruled that a child born to a married woman through a father not the woman's husband is illegitimate and that the wife's act constituted adultery, regardless of the husband's consent.

However, it also found that the husband's consent did make him liable for the child's support on an implied contract theory, and he was equitably estopped from denying his obligation.<sup>27</sup>

A recent decision of a New York court held that the father of a child born after AID with his consent is a "parent" whose consent is necessary for the adoption of that child by the mother's second husband.<sup>28</sup> Refusing to decide the case on the basis of the strong presumption of legitimacy of children born during a marriage, the court rejected Gursky as not persuasive and as "the only published decision which flatly holds that AID children are illegitimate." <sup>29</sup> The court focused instead on the critical issue: the child, rather than the parents, deserved protection. "It serves no purpose whatsoever to stigmatize the AID child." Thus the court indicated that any child whose parents, during their valid marriage, consented to AID is just as legitimate as a naturally conceived child of that same marriage.

In the Sorenson case discussed earlier,<sup>31</sup> which was a criminal case, the defendant, by written agreement, had consented to the artificial insemination of his wife. After a subsequent divorce, the wife, due to illness, became unable to support the child, and the district attorney of her county demanded child support payments under under Section 270 of the Penal Code from the defendant. In the ensuing criminal prosecution for nonsupport, the defendant pleading that he was not the father of the child.

The California Supreme Court held that the defendant was the lawful father of the child born to his former wife, that the child was conceived by artificial insemination to which the defendant had consented, and that his conduct carried with it an obligation of

support within the applicable statutory meaning.<sup>32</sup> The court stated that the term "father" must be broadly interpreted. It should not for these purposes be limited to the biological or natural father as those terms are generally understood, but rather tied to an evaluation of whether the legal relationship of father and child exists. Paternity, then, is established beyond a reasonable doubt when it is shown that a husband, unable to accomplish his objective of begetting a child, purchases semen from a donor and proceeds to use it to inseminate his wife.<sup>33</sup> The court said that, although both legitimate and illegitimate minors have a statutory right to support from their parents, "no valid public purpose is served by stigmatizing an artificially conceived child as illegitimate."<sup>34</sup> The court therefore held the defendant to be the lawful father of the child, liable for his support.

A related legal issue is whether artificial insemination babies may inherit from their "fathers." It has been resolved in the past by reference to the legitimacy of the child. A legitimate child could inherit, while the illegitimate child could not.

However, recent cases are beginning to reduce some of the distinctions between the legitimate and illegitimate child.<sup>35</sup> Some cases have held that this trend extends to inheritance rights and that denying the illegitimate child the same right of inheritance as his legitimate sibling results in a denial of equal protection of the law.<sup>36</sup> The abolition of these distinctions, combined with the trend toward finding AID children to be legitimate, will likely result in inheritance rights of AID children being the same as those of "normally conceived" children.



However, the mere adoption by some modern courts of a liberal interpretation does not remove artificial insemination and related reproductive technology from the context of present adultery and legitimacy laws. Yet, since these reproductive techniques do not belong in the "immoral" category of actions which these concepts are meant to address, it is anomalous to consider them as such. While there are dangers associated with these reproductive methods, they are qualitatively different than those involved in adultery and illegitimacy. Nevertheless, at the present time, these broad questions must be answered by the legislature.

A number of states have passed legislation to deal with this issue, although the legislative response has been minimal.<sup>37</sup> In 1964, Georgia became the first state to pass a statute legitimizing children conceived by artificial insemination if both husband and wife consent in writing.<sup>38</sup> Oklahoma<sup>39</sup> and Kansas<sup>40</sup> have statutes which, apart from legitimatizing the artifically conceived child, provide for the filing and safeguarding of the requisite consent forms. Arkansas law provides that an AID child is to be treated as the child of its mother and her consenting husband for purposes of intestacy.<sup>41</sup> Consent, under the statute, is presumed unless there is clear and convincing evidence to the contrary. Maryland<sup>42</sup> and North Carolina<sup>43</sup> also have statutes legitimatizing artifically conceived children. New York legislation states that, if a married couple consents in writing to artificial insemination and a physician certifies the procedure, the child is deemed legitimate for all purposes.<sup>44</sup>

After the Sorenson case, California passed a statute declaring that children born by means of artificial insemination are legitimate if the husband has consented in writing and the birth has occurred

within the prescribed period of time, and that the child's legitimacy is not affected by the marriage being declared void, invalid, or adjudged a nullity.<sup>45</sup> In addition, another California law maintains that the husband of the child's mother is liable for his support.<sup>46</sup>

To the extent that IVF does not differ significantly from artificial insemination, it is likely that family law will treat the two similarly. Legal clarification of artificial insemination is thus a necessary prerequisite for regulating IVF.

When the husband provides the sperm and the wife the ovum, the legal situation is analogous to that of homologous artificial insemination in that the resulting child is the biological offspring of both husband and wife.

When a donor provides the sperm used in the IVF process the situation is so similar to heterologous artificial insemination that the same laws and legal principles should apply and determine the rights of the parties. The situation becomes more complex if the ovum also comes from a donor, or if the ovum comes from a donor and the sperm from the husband. There has never before been any question as to the identity of the mother of a child when it is born, because birth itself has generally been considered conclusive proof of motherhood. When the ovum comes from another source, is fertilized and transferred into the wife's uterus, the question becomes whether contributing the ovum or carrying and giving birth to the child entitles a woman to claim motherhood. In order to avoid the problems which have been raised with AID, it may be necessary to have a state statute which provides that the wife will be deemed to be the mother

of the child for all legal purposes. In general, though, it may be said that the situation is so similar to AID, that the same rules and principles would apply.

The most difficult situation is that in which the wife's ovum is fertilized by the husband's sperm in vitro and the embryo is transferred into a third party, or "hostess", who carries the child for the duration of the pregnancy and then gives birth to it. The resulting infant would be the biological offspring of the woman who contributed the ovum and gestationally the offspring of the "hostess" who bore it.

Numerous legal problems would be raised by such a procedure. For example, if the "hostess" were being monetarily compensated for her services, what would happen if payments are missed? Does the child then belong to the "hostess"? Can the "hostess" choose to abort in such a situation? May the couple place restrictions on the "hostess", such as those related to diet, drugs taken, activities engaged in, physician chosen, number of doctor visits, etc.? Can the couple require the "hostess" to undergo amniocentesis? If a defect becomes known, can the couple require her to have an abortion? Can the couple refuse to take the child at birth? Can the "hostess" decide to abort for health reasons? Is the couple liable for the extraordinary costs of a difficult pregnancy? What if the "hostess" refuses to release the child to the custody of the couple upon birth? What if she claims that she had aborted earlier and that this child is hers? Under what circumstances might the "hostess" be left with the child and be liable for its support? What if the couple dies prior to the birth? What are the rights of the child, if any, against the "hostess", such as right to support or right to inherit?

These issues indicate the necessity of, at the very least, having a clearly drawn contract which anticipates some of these problems and specifies the rights and duties of each of the parties involved. However, in order to fully protect all interests, it would seem the wisest course to enact a state statute which had a scheme which encompassed the following.

First, all parties must consent in writing to the procedure. The "hostess" must agree that the baby will be legally the child of the couple who contribute the germ cells and that her rights to the child will terminate at birth. To protect her health, it must be clearly established that, should the pregnancy in any way endanger the "hostess" physically, an abortion will be immediately performed.

In order to protect the privacy of all concerned, the "hostess" should remain anonymous to the couple and vice versa. As with the case of AID, only the physician should know the identity of all parties concerned. A new birth certificate should be issued with the names of the biological parents of the child. Any hospital records and the original birth certificate with the name of the "hostess" on them should be sealed by law and be available only upon a court order.

The variances from the common conception of parenthood in these processes are similar to those of adoption. The couple who raise the child, care for him, support him, and are legally responsible for him, are his legitimate parents. As in other similar situations, the stigma of illegitimacy should not attach to the child. It is important that court challenges similar to those in AID cases be avoided with IVF. Accordingly, state statutory action is critical to legitimize children born of IVF, thereby resolving the basis family law problems.



This is especially important since IVF will eventually allow a departure from the traditional family concept even greater than artificial insemination, and the law must be ready to respond.

#### IV. Potential Civil and Criminal Liability

##### A. Liability for Birth of Defective Child

There is as yet an unknown possibility that IVF infants will be born with defects which could be attributable to the use of the reproductive technique.<sup>47</sup> There are several theories of tort law which could be brought to bear on the resolution of the problem of compensation for these injuries.

##### 1. Prenatal or preconception injury

Although contrary to early tort law,<sup>48</sup> every state currently allows recovery in tort for prenatal injuries.<sup>49</sup> A number of recent cases also permit recovery for preconception infliction of personal injuries.<sup>50</sup> An obvious prerequisite to this type of action is the live birth of the child.<sup>51</sup>

The earliest cases in this area established viability as the test for recovery.<sup>52</sup> This seemed to be based on the evidence problem of proving that the defendant's actions actually caused the complained-of injuries. However, the modern trend is to permit recovery without regard to whether the infant was viable at the time of injury.<sup>53</sup> Yet the plaintiff is still faced with the difficult chore of proving the applicable standard of care and proximate cause.<sup>54</sup>

## 2. Wrongful Life

A severely defective IVF child could bring a "wrongful life" suit against his parents and/or physician for giving him life. However, recovery upon such grounds is usually denied.

For example, in the 1963 Illinois case of Zepeda v. Zepeda, an illegitimate son sued his putative father for fraudulently inducing his mother to have sexual relations upon the promise of marriage. The father was already married. The child sued for damages for deprivation of a normal homelife, deprivation of rights of inheritance, and for having to suffer the stigma of being born illegitimate. The court denied the plaintiff relief because "recognition of the plaintiff's claim means creation of a new tort: a cause of action for wrongful life."<sup>56</sup>

Three years later, a New York court considered the case of Williams v. State,<sup>57</sup> in which an illegitimate daughter brought suit against the state for deprivation of property rights, deprivation of a normal childhood, and deprivation of proper parental care, support and rearing, in addition to having to bear the stigma of illegitimacy. The child's mother was a patient in a state mental institution when she was raped by another inmate. The woman became pregnant and gave birth to the plaintiff. The court dismissed the complaint, stating

that "[b]eing born under one set of circumstances rather than another or to one pair of parents rather than another is not a suable wrong that is cognizable in court."<sup>58</sup> The concurring opinion was based upon the question of damages.

Damages are awarded in tort cases on the basis of a comparison between the position the plaintiff would have been in, had the defendant not committed the acts causing the injury, and the position in which the plaintiff presently finds herself. The damages sought by the plaintiff in the case at bar involve a determination as to whether nonexistence or nonlife is preferable to life as an illegitimate with all the hardship attendant thereon. It is impossible to make that choice.<sup>59</sup>

The court, by construing the child's cause of action to be whether it is better to never have been born at all than to have been born in the condition in which the plaintiff finds himself placed a tremendous obstacle in the way of this avenue of relief.

Similarly, in the case of Nellis v. Chicago Wesley Memorial Hospital, a husband went to the defendant hospital for a routine check-up. A physician in the hospital discovered he had thalassemia minor. In other words, he was a carrier for this deadly disease. As a precaution, the hospital requested that his wife come in for a test also, to determine whether she, too, was a carrier. The hospital found she wasn't. The wife became pregnant and delivered a baby with thalassemia major. The wife was a carrier of the disease as well, although the hospital had failed to detect this. The baby was a

homozygous affected offspring, of which there was 25 percent probability. The child brought suit against the hospital for wrongful life. The case was dismissed for failure to state a cause of action.

Thus, although a few cases have espoused this theory, as yet it has rarely been recognized as a viable basis for recovery.<sup>61</sup> Indeed, the wrongful life concept has been judicially accepted in only one decision.<sup>62</sup> It seems that the basic reason for denying recovery in this type of case is the impossibility of measuring damages. Such determination would require the court to make a value determination that no life at all is better than a life with handicaps, which is a calculation the courts are reluctant to undertake.

There is some indication that the wrongful life theory may be on the verge of legal acceptance. This possibility has important implications for birth defects following the use of IVF. However, the plaintiff would still be faced with the difficult task of proving that such defect was caused by the use of the reproductive technology.

### 3. Wrongful Birth

Another line of cases which has possible ramifications for children born with defects as a result of IVF is that in which the woman who gave birth to the child brings the cause of action. Cases falling into this category include a suit by the parents of a deformed child against the mother's



physician for his failure to diagnose rubella during the course of the pregnancy.<sup>63</sup> The child was born with defects of the brain, speech, sight, hearing, kidneys, and the urinary tract, among others. In their malpractice suit, the parents claimed damages for their physical, emotional, and financial suffering. The Texas Supreme Court said that their claim stated a cause of action.<sup>64</sup>

Similarly, a New York court has held that a malpractice claim against a doctor for not diagnosing a pregnancy in time for an abortion states a cause of action.<sup>65</sup> There was a strong dissent in the case based on the premise that "parents should not be able to enjoy the pleasure and comfort of their child and also seek compensation for its birth."<sup>66</sup>

A Michigan court ruled that a woman has a cause of action against a pharmacist for mistakenly filling a prescription for the contraceptive Norinyl with a different drug, Nardil.<sup>67</sup> The woman was suing for medical expenses attendant upon birth, the pain and suffering incident to childbearing, plus the cost of raising the child.<sup>68</sup> Finally, an Illinois court concluded that when a wife's physician orally agreed to sterilize her husband so as to prevent procreation, the operation was performed and they resumed sexual relations and subsequently gave birth to a third retarded child, the complaint stated a cause of action.<sup>69</sup> In particular, this last action very definitely represents the modern trend in this area.

In general, usual standards of medical malpractice would be applicable in this area. However, as discussed in

reference to the wrongful life suit, the problem of proving causation is extremely complicated. A certain number of conventional births result in defective infants, and it might be difficult to prove that the IVF process itself was responsible. If the parents have been fully informed in advance of the procedure and the risks involved and have consented in an informed manner to the procedure in the face of those risks, the parents' action would be even harder to prove.<sup>70</sup>

#### B. Liability for "termination" of IVF Conceptus

It is certain that a significant number of conceptus "terminations" will be attributable to the use of IVF. What are the potential legal ramifications of this occurrence?

##### 1. Criminal Law

Under present technology IVF involves the deliberate fertilization of a human egg, and in the course of the process, the necessary "termination" of fertilized eggs.<sup>71</sup> The "termination" may occur a few moments after conception or a number of days thereafter. It may occur intentionally, by mistake, or by negligence. However, if work in the area of IVF is to continue, it is a fact that a great many of these conceptuses will be destroyed. What is the criminal law implications of this?<sup>72</sup>

The destruction of human offspring is legally defined as prolicide.<sup>73</sup> Prolicide is divided into two subjects, feticide and infanticide.<sup>74</sup>

Feticide is defined as the destruction of the fetus, whether in utero or in vitro.<sup>75</sup> Historically, the Greeks and Romans practiced feticide without penalty.<sup>76</sup> The common law followed the precedent set by the Greeks and Romans, until until that point of pregnancy when the embryo became "quick."<sup>77</sup> A "quick" child was distinguished at the first uterine movement of the fetus.<sup>78</sup> The distinction of "quickness" was an important one under the common law, for it determined the nature of the abortion act. Prior to "quickening", the fetus was considered a part of its mother and no crime resulted from its destruction.<sup>79</sup> After "quickening", however, feticide resulted from the abortion act.

Blackstone explained that before any degree of homicide could occur, there had to be a person, a "reasonable creature in being", to be the subject of a homicide, and a fetus, whether "quick" or not, had never met that criteria.<sup>80</sup> Thus, it is clear that although the common law looked upon the destruction of a "quick" fetus with disfavor, it did not accord even the "quick" fetus the status of a human being,<sup>81</sup> and apparently afforded no status whatsoever to the pre-"quick" fetus. Accordingly, it is an easy conclusion that, were the common law the rule today, "terminating" an IVF conceptus would not be a crime of any degree, since there would be no evidence of "quickening".

However, how does American statutory and case law view the termination of a conceptus? In American jurisprudence, the initial feticide statutes continued the English distinction of "quickness", dealing harshly with feticide after "quickening" and being lenient with feticide before "quickening".<sup>82</sup> Beginning in the middle 1800's, however, the "quickness" distinction began to disappear from the statutory law of most states, and the degree of the offense and the penalties attached thereto were made more severe.<sup>83</sup> Some states even classified feticide as a homicide, manslaughter.<sup>84</sup>

The statutory trend was also reflected in the case law. In the 1850 case of Mills v. Commonwealth,<sup>85</sup> the Pennsylvania court held that "quickness" was not a necessary element in the crime of abortion.<sup>86</sup> Almost one hundred years later, in the case of Hall v. People,<sup>87</sup> the Supreme Court of Colorado held that the crime of feticide occurred with the destruction of the fetus at anytime before birth. A similar holding was reached by the Supreme Court of Nebraska in the case of Hans v. State.<sup>88</sup>

It is clear that the arbitrary and technical distinction between the terms "embryo" and "foetus" are not recognized by the law. The terms are practically interchangeable and refer to an unborn child, in ventre sa mere. It is obvious the Legislature used these terms in their ordinary and commonly accepted meaning, and when it used the term "foeticide" it meant the unlawful destruction of an unborn child, in ventre sa mere, at any stage of gestation.<sup>89</sup>



With the concept of "quickness" having been completely abandoned at this point, a charge of feticide would stand for the destruction of a fetus or an embryo. Under this approach, the "termination" of an IVF conceptus would seem to be feticide. The only possible avenue for escaping criminal liability might be the qualifying phrase, in ventre sa mere, or "in the mother's womb".<sup>90</sup> The IVF conceptus at this point would not be in the mother's womb.

However, the American law of feticide, as developed by statutory and case law dating from the middle 1800's, was abrogated by the United States Supreme Court decision in Roe v. Wade.<sup>91</sup> The Court held unconstitutional the feticide statutes proscribing abortion at any stage of gestation. Basing its decision on the mother's right to privacy, the Court explained that the statutes, in restricting a woman's right to terminate her pregnancy at certain stages, violated the due process clause of the Fourteenth Amendment. The Court acknowledged, however, that the mother's right to terminate her pregnancy was not an unqualified right.<sup>92</sup> The decision differentiated the extent of this right during the three gestational trimesters. The decision to terminate the fetus during the first trimester must be solely that of the mother and her physician.<sup>93</sup> During the second trimester, a state may regulate the abortion procedure only to insure maternal health.<sup>94</sup> During the final trimester of gestation, a state may protect fetal life by prohibiting abortion;

except where it is necessary to preserve the health of the mother.<sup>95</sup> With the decision in Roe v. Wade, the law of feticide has come full circle, for the protection the Supreme Court afforded a third trimester fetus is analogous to the protection the early common law afforded a "quick" child. There is no crime of any degree for the destruction of a fetus prior to the third trimester, just as there was no crime of any degree for the destruction of a fetus prior to "quickening". As a result of the Roe decision, the "termination" of a conceptus clearly could not be feticide.

Infanticide has been defined as the killing of an infant after its birth.<sup>96</sup> It is the felonious taking of the life of a newborn child, which constitutes the crime of murder.<sup>97</sup> The crucial element in a case of infanticide is the birth of the child. As stated in the case of Gilpin v. Gilpin:<sup>98</sup>

It [the birth of the child] determines the distinction between the crimes of foeticide and infanticide. The former, the destruction of the life of the foetus; infanticide, the felonious taking of the life of a newborn child. The killing of a foetus in utero, is manslaughter; the killing of a child after its birth is murder.<sup>99</sup>

Determining exactly what constitutes the "birth" of a child has, however, been something of a problem. Precisely defining infanticide and accurately identifying the elements of that crime have significance when contemplating the criminal nature, if any, of the "termination" of an IVF conceptus, for the IVF conceptus begins life apart from the

body of the mother. Yet it cannot be literally said that the conceptus has been "born alive". Nevertheless, the conceptus is living apart from the body of the mother and in this sense is somewhat analogous to a viable child.

A viable child is in essence a fetus that is capable of an existence independent of the mother. In the case of an IVF conceptus, "viability" occurs at conception. It is not only capable of an independent existence, but maintains an independent existence. Yet it is still a fetus because it has never been "born alive". The viability analogy is of importance due to the Supreme Court's decision in Roe. The Court held that the state's police power could include a compelling interest in the protection of fetal life at the stage of viability, such that the state could regulate and even proscribe the destruction of a fetus at that stage.

However, in the final analysis, it is unlikely that the "termination" of an IVF conceptus would fall within the homicide statute. Such a statute requires the killing of a person.<sup>100</sup> Most jurisdictions have held that a fetus, even a viable one, is not a person within the meaning of these statutory schemes.<sup>101</sup> Thus, the "termination" of an IVF conceptus would not be murder.

## 2. Civil Law

What are the implications for potential civil liability for the "termination" of an IVF conceptus?<sup>102</sup>

Those parties who may be defendants in this type of action are the parents, physician/researcher, and research institution.

First is the situation in which the researcher destroys the conceptus with the consent of the parents. As long as the parents have received sufficient information to give their informed consent to the "termination", the parents would not be able to successfully sue the researcher or the institution housing his research.<sup>103</sup> It would also seem that there should not be any liability by the researcher or consenting parents to the conceptus' estate for his "termination". Considering the situation as analogous to abortion, it may be argued that, since the voluntary destruction of an implanted conceptus is abortion, the "termination" of an unimplanted conceptus may also come within the same "right of privacy" of the mother. Similarly, an analogy may be made to the use by a woman of an intrauterine device (IUD) for birth control purposes. While again a difference is that the situation of an IUD takes place within a woman's body, it is nevertheless similar in that it deals with a fertilized egg which is voluntarily "terminated" by the woman by not permitting implantation. Both abortion, within certain legal limits, and the use of an IUD are rights which a woman may exercise without liability to the "entity" "terminated" in this manner. Accordingly, by analogy, it is a logical extension to maintain that the parents and researchers should not be civilly liable for the voluntary "termination" of the IVF conceptus.



However, there are situations in which the "termination" of the IVF conceptus may lead to civil liability. Such liability may theoretically be imposed on the researcher for the negligent "termination" of the conceptus. However, in a practical sense, a suit of this type would be extremely difficult for the plaintiffs to prove. Because of the experimental nature of the IVF procedure at the present time, a major obstacle to overcome would be the establishment of a standard of care by which to judge the actions of the physician.<sup>104</sup> In addition, it would also be difficult to establish the necessary causal link between the researcher's actions and the "termination" of the conceptus.<sup>105</sup>

Finally, liability to the parents may be possible for the intentional and non-consented-to "termination" of the IVF conceptus by another party. While the legal status of the pre-implantation conceptus is unclear, it may be appropriate to consider it the "property" of the couple. Thus, damages could still be awarded for its destruction if it were found to have occurred as the result of an intentional tort. Such a damage award would indicate that, although the conceptus is not a legal "person", its potential for development into a human being gives it a value greater than other tissue. Thus, it may seem proper to hold the researcher to a special standard of care in regard to IVF.

The first law suit of this type involving IVF has recently been decided in New York. John and Doris Del Zio bought a \$1.5 million damage suit against Manhattan's Columbia-Presbyterian Medical Center and its Chief of Obstetrics and Gynecology, Dr. Raymond Vande Wiele<sup>106</sup> Despite several operations, Mrs. Del Zio had apparently been unable to become pregnant because her tubes had been blocked and partially destroyed by disease. Eggs were obtained from Mrs. Del Zio and bathed in follicular fluid that contained bits of tubal mucosa. They were exposed to Mr. Del Zio's sperm in a culture medium by Dr. Landrum Shettles.<sup>107</sup> However, prior to implantation, Dr. Vande Wiele destroyed the culture, contending that the procedure was risky, that an IVF child might be born with severe defects, that Dr. Shettles lacked the skills to undertake it, and that it had not been approved by the hospital's committee on human experimentation.<sup>108</sup> Mrs. Del Zio claimed that terminating the procedure without the consent of she and her husband denied them their last opportunity to have a child, damaged her both physically and psychologically, upset her sex life, and jeopardized her marriage.<sup>109</sup> A trial court awarded Mrs. Del Zio \$50,000 in damages for emotional distress and awarded her husband nominal damages.<sup>110</sup>

In general, however, the possible bases for a cause of action of this type are unsatisfactory. For example, a suit for the intentional infliction of emotional distress is most likely to be unsuccessful, because of the difficulty in proving the "outrageousness" of the other party's

conduct,<sup>111</sup> and in demonstrating that the parents have suffered harm from the emotional distress caused by the "termination" of their conceptus.<sup>112</sup>

There would be similar problems in bringing an action for wrongful death. Every state permits recovery if the child, injured as a result of some individual's wrongdoing, does not survive to bring his own action.<sup>113</sup> These suits for "wrongful death" are entirely matters of statutory law and are not based on common law or constitutional rights.<sup>114</sup> Neither the difficulty in determining damages nor the problem of proving causation has been considered sufficient to bar this particular type of action.

However, there is still disagreement among jurisdictions concerning whether or not a live birth is required in order to maintain a wrongful death action. Several states require a live birth, asserting that there has been no harm to a legally-recognized "person" until the fetus is born alive.<sup>115</sup>

Nevertheless, the modern trend is to permit an action for the wrongful death of a viable fetus regardless of whether it is born alive.<sup>116</sup> Beyond that, Georgia permits such an action for children damaged when not yet viable but only "quick".<sup>117</sup> In order to allow recovery in these cases, courts have held that the unborn fetus is a "person" or "minor child" as a matter of statutory construction.

A fairly recent case which discusses the fetus' statutory status is Eich v. Town of Gulf Shores.<sup>118</sup> In it, the Alabama Supreme Court held that the purpose of the

Alabama wrongful death statute was to preserve human life, and that therefore a live birth was not a prerequisite to liability.<sup>119</sup> The court indicated that it considered the "live birth" requirement to be illogical, since under such a standard, a tortfeasor's liability depends not on the seriousness of his conduct, but on whether the injured child is able to survive his injuries for at least a moment after birth. Thus, a wrongdoer is rewarded if his conduct kills a fetus immediately.<sup>120</sup>

However, even with the modern trend toward permitting recovery for the wrongful death of a viable or quick fetus, it is still unlikely that parents of an IVF conceptus could make successful use of this cause of action, since the probable "termination" point of the conceptus would be prior to implantation, which at the present time is certainly before the stage of viability or quickness.

#### IV. Compensation for Harm

It has been demonstrated in the preceding section that existing common law remedies are inadequate to compensate those harmed by involvement in the IVF process. Accordingly, another approach should to be undertaken in order to meet this outstanding need.

##### A. Strict Liability

A possible solution to this dilemma would be the application of the doctrine of strict liability.<sup>121</sup> The basis for such a suit, either by or on behalf of the IVF child, is the notion that liability may be imposed although the defendant is not negligent in that he has not deviated from the appropriate



standard of care.<sup>122</sup> Such liability is generally imposed for those activities deemed abnormally dangerous, as IVF would be considered at the present time.<sup>123</sup> Imposition of the doctrine evidences a societal decision that, while a particular enterprise will be tolerated, it is of a type which should carry its own burden in society, so that if an individual is injured because of it, the loss will be shifted to the party best able to carry it.<sup>124</sup> Thus, the IVF researcher would be proceeding at his own risk, since he has exclusive control of the experimental situation, and would be held liable without fault if an injury were to occur.

There is a difficult policy choice to make here. Imposition of strict liability might have an unwanted chilling effect on the development and continuation of IVF research. However, I believe the analysis balances in the favor of application of the doctrine.

Since strict liability responsibility is limited to those damages which are the result of the extraordinary risk involved, the IVF researcher would not be liable for every defect in an IVF child.<sup>125</sup> Accordingly, he would not be responsible for the consequences of an "act of God" or an independent unforeseeable act by a third party.<sup>126</sup> Beyond that, through resort to liability insurance, the costs could be distributed among IVF researchers, or even among all recipients of medical services.<sup>127</sup>

Finally, to keep costs at a reasonable level, limits may be placed on the amount of damages recoverable under the theory.<sup>128</sup>

B. Compensation Fund

As an alternative to the imposition of strict liability, or as an additional compensation mechanism, a compensation fund might be a viable option.<sup>129</sup> This is particularly true as long as IVF is an experimental procedure, as is currently the case, and any work in the area would most likely be part of a research protocol. In such a situation, not only would the parents and potential IVF child benefit, future parents and IVF children, as well as society as a whole, would be the beneficiaries of the knowledge gained as a result of undertaking the procedure. In this sense, it is no longer logical to speak in terms of individual tort liability, but rather becomes necessary to discuss societal responsibility.<sup>130</sup> As the ultimate beneficiary and implied endorser of such experimentation, society may be expected to assume certain burdens.

In the field of tort law, many activities are permitted which are known to cost lives since it has been determined that to make these activities safer or to abstain totally from them would cost too much. Much of the control over the taking of human life is determined by the "market system", in which human beings are given a money value, the activities which injure people pay the victims, and society coldly decides whether it is cheaper to make the activity safer or to pay the cost of injuries.

Thus, the control mechanism takes into account both the value of lives taken as well as the cost of saving them.<sup>131</sup>

The area of IVF research, however, is concerned with risking harm, including death or "termination", in order to benefit future others as well as the involved parties, not in order to save money. However, there is presently no control system analogous to that in the accident field which allows a sufficient balancing of these interests.<sup>132</sup> This could be accomplished by setting up a mechanism by which those injured in the IVF process are compensated without regard to fault.

In a very broad sense, nonfault liability encompasses any compensation system that uses criteria other than fault to determine benefits coverage. However, in the context of this discussion, I intend the term to indicate those schemes which use a social security system as the major source of compensation. In essence, such a mechanism has government management and funding, and uses a criteria for compensation that is often more closely related to the need for benefits than to the causes of the need.<sup>133</sup> Worker's compensation is generally considered a special system of social security.<sup>134</sup>

Accordingly, in the IVF area, indemnification should be made from a federal compensation fund. Otherwise, there might be situations in which both the experimenter and sponsoring institution lacked sufficient resources to adequately compensate an injured party. Additionally,

since the system is based on a "non-fault" premise, the researcher and institution are blameless, and imposing financial responsibility on them could make them unwilling to accept the risk of liability, thereby curtailing the amount of IVF research done, as mentioned above.

Beyond this, the federal government, if it decides to support this type of research, will have therefore encouraged such an undertaking. Many of the benefits of IVF experimentation accrue to society as a whole, and not to an individual component within it, be that component an institution or a state. In addition, compensation is a critical matter of national concern, and should therefore be dealt with by a uniform federal policy, not subjected to the whims of individual states.

To finance this fund, one could require the payment of premiums from IVF experimenters or research institutions, or surcharge the medical bills of the sick. In the alternative, one could provide the necessary money through general revenues. Since the taxing structure available to the federal government provides the most efficient means of allocating the costs to society, and since the results of IVF research will ultimately benefit a large segment, if not all, of society, it is logical to distribute the burden of costs through the use of general revenues.

Costs should be covered for injuries incurred through participation in IVF research. It would be irrelevant whether the cause of the damage was fault on the part of the experimenter or a nonnegligent accident.



However, it is often difficult to determine when an individual's injury is truly attributable to participation in the experiment. For example, are the problems of a defective IVF child the result of the reproductive process or of a genetically-inherited trait. This is essentially the same problem faced by proponents of no-fault medical malpractice insurance, who are running into serious difficulty in developing a scheme for determining the compensable event.

However, since the underlying rationale for indemnification of IVF victims is different than that forming the basis for compensating patients injured by medical malpractice in the course of conventional therapy, in that the participation in IVF research may be said to ultimately benefit society, the solution to this problem in the IVF area should perhaps not create the same obstacle to implementation of the program. Since it would necessitate a large expenditure of administrative funds to determine the compensable event, it might be preferable to add those resources to the money allocated for direct compensation. Even though certain individuals may benefit from a windfall, it would be better to avoid the entire causation dilemma. Thus, compensation should be available in all instances in which the damage is not clearly unrelated to participation in the IVF procedure. Eligibility would therefore depend only on a showing of participation in the IVF process coupled with minimal proof of injury. Since participation is of

benefit to society, the plan should favor compensation of the individual.

One of the most difficult problems is determining the amount of compensation which an individual will receive. The fund should cover the cost of medical expenses and the expense to the individual of whatever damage was caused by participation in the IVF procedure, such as future rehabilitation and special education costs for a defective IVF child. In essence, the compensation for a defective IVF child should be measured by the costs of placing him in the position of a "normal" child, to the extent that money damages is able to achieve this. However, should this recovery be individualized depending on a determination of the actual losses sustained and requiring a rather extensive hearing on the matter, or should it be provided by a schedule, as in worker's compensation. It would seem that, in an area in which fault determinations have been rejected, a schedule of payments related to average costs does not seem an unreasonable way to fairly fulfill society's obligation.

One potential problem with a program of federal government indemnification should be noted. There is a danger that there will be a lack of a financial incentive on the part of IVF researchers which would otherwise have prevented them from pursuing risky or hazardous aspects of IVF research. One way of determining whether there is enough confidence in a proposed procedure is to assume payment for the individuals who may be injured by it.

If there is not, it is reasonable to assume that the particular procedure is too risky. Thus, requiring compensation of those injured by IVF experimenters would cause the full cost of such research to be placed on the parties carrying out the research. A decision to proceed with the procedure would require a conscious consideration of the risks, converted into money, forcing a determination of whether the procedure was worth it, and whether there was a safer, alternate way of achieving the same results.<sup>137</sup>

However, this controversy appears to be resolvable. The Ethical Advisory Board, as well as institutional review committees at individual facilities, are active in determining which in vitro fertilization experiments are unjustified. In addition, the indemnification system could be set up so that institutions with much higher than average rates of compensable injuries would pay losses directly, eliminating the institution's eligibility to participate in the program. This would serve to reinforce the activities of the review committees.<sup>138</sup>

#### V. Government Regulation of IVF

IVF is presently an experimental technique. Accordingly, current government regulations which govern human experimentation would also be applicable to research in the IVF area. However, there is a further complicating factor with IVF research which would seem to call for additional regulations being developed to prevent the unnecessarily hazardous use of the procedure.

Since the intent of the IVF procedure is to produce a healthy child, it would seem that the state may properly develop guidelines to protect the pre-implantation conceptus. The government, under the mantle of its parens patriae power, may regulate a technology for the benefit of those affected by it. The structure of such a regulatory mechanism would be mandated by the concerns for maternal and conceptus health, safety, and welfare.<sup>139</sup>

Beyond that, risk to the IVF conceptus is not easily quantified. However, it seems clear that a certain number will be destroyed and that some will develop into defective children. Accordingly, we become involved with the concept of consent. Who may "consent" for the potential conceptus, or are we even concerned with the application of that doctrine on the part of that entity? Does the resolution of this question have an effect on the ability of the couple to make the decision to attempt to achieve pregnancy by means of IVF? Would the couple merely be considered to have exercised their own right of privacy, or might they also be considered to have exercised "proxy" consent on behalf of a third party, the conceptus?<sup>140</sup>

Briefly, proxy consent may only be granted or withheld on the sole basis of the welfare of the party for whom consent is being exercised.<sup>141</sup> The judgment of the consent-grantor regarding the other individual's best interest is not always conclusive, and the government will intervene to protect the other's welfare. Therefore, the state, exercising its ultimate responsibility under the doctrine of parens patriae, will intervene when the question arises as to whether this "best interest" standard has been met.<sup>142</sup>



Assuming that the conceptus is the third party in the IVF process, then the risks in the procedure become critical in the government's ultimate review and protection of the best interests of that third party.<sup>143</sup> Presumably the state could act to protect these interests and regulate the use of IVF.

#### A. Current HEW Regulations

Proposed regulations for the protection of human subjects to be generally applicable to all HEW grant-supported activity were published in November, 1973.<sup>144</sup> This draft document proposed a moratorium on IVF research until the safety of the technique has been demonstrated as far as possible in sub-human primates, and the responsibilities of donor and recipient 'parents' and of research institutions and personnel have been established."<sup>145</sup> It also recommended that all IVF proposals be approved by one of the proposed Ethical Review Boards (the current Ethical Advisory Boards).<sup>146</sup> However, the draft did not provide specific standards by which the Board's decision was to be guided.<sup>147</sup>

<sup>148</sup>  
A revised draft was published in August, 1974, with final regulations being promulgated in 1975.<sup>149</sup> The rules again do not provide specific regulations governing research with unimplanted IVF conceptuses. The document also does not establish the originally proposed moratorium on IVF research. It does follow the earlier drafts in leaving the resolution of issues in the IVF area to the Ethical Advisory Board.<sup>150</sup> It was noted that experimentation on implanted IVF conceptuses would be governed by the fetal research regulations.<sup>151</sup>

Briefly, the fetal research regulations provide for the establishment of two ethical advisory boards, one advisory to the Public Health Service and the other advisory to all other agencies and components of HEW concerning applications for research on

fetuses.<sup>152</sup> In addition, the regulations expand the functions of Institutional Review Boards in local hospitals and similar institutions in connection with such activity.<sup>153</sup> No research award may be made by HEW until the appropriate reviewing bodies certify the research application.<sup>154</sup> The boards must determine that adequate consideration has been given to the manner in which potential subjects will be selected, and must make sure that an adequate mechanism exists for monitoring "the actual informed consent process".<sup>155</sup>

General limitations are placed on all research activity.<sup>156</sup> Studies on animals and nonpregnant individuals are required before fetal research may be undertaken. When nontherapeutic research is conducted, the risk to the fetus must be minimal. If the research is therapeutic and conducted on either the mother or the fetus, the risk to the fetus must be the least possible consistent with achieving the objectives of the research.<sup>157</sup> Individuals engaged in the research activity are to have no part in any decision as to the timing, method, and procedures used to terminate the pregnancy or any determination of the viability of the fetus at termination of the pregnancy. No procedural changes which may cause greater than minimal risk to the fetus or the pregnant woman may be introduced into the procedure for terminating the pregnancy solely in the interest of the activity. In addition, no inducements, monetary or otherwise, may be offered to terminate pregnancy for the purpose of the activity.<sup>158</sup>

The regulations specifically permit in utero therapeutic research, and allow in utero nontherapeutic research as long as the risk to the fetus is minimal and the purpose of the research is the development of "important biomedical knowledge which cannot be obtained by other means".<sup>159</sup> Prior to conducting fetal research the consent of both parents is required, except that the father's consent need not be obtained if his identity or whereabouts cannot reasonably be ascertained, he is not reasonably available, or the pregnancy resulted from rape.<sup>160</sup>

Prior to conducting research with ex utero fetuses, a person not involved with the research must determine if the ex utero fetus is viable.<sup>161</sup> This determination need not be made prior to conducting the research if there is "no added risk" to the fetus as a result of the research and it is for the development of important biomedical knowledge that cannot be obtained by other means. If an ex utero fetus is determined to be viable, it is subject to the regulations that control research with children. As a general rule, vital function of the nonviable ex utero fetus may not be artificially maintained. This may be done where the purpose of the research is to develop new methods for enabling fetuses to survive to the point of viability.<sup>162</sup> This is true even though the fetus-subject will not benefit from this research. Under no circumstances do the regulations permit activities that would cause termination of fetal heartbeat or respiration. Finally, any nontherapeutic research that is done must be for the purpose of developing important biomedical knowledge that cannot be obtained by other means.<sup>163</sup> The consent requirement by the mother and father is the same as for in utero research.<sup>164</sup> Other

provisions place limits on research activities involving the  
dead fetus, fetal material, or the placenta<sup>165</sup> and research  
carried out in connection with abortion.<sup>166</sup>

However, these fetal research regulations do not per se  
apply to IVF research, since the rules define fetus as "the  
product of conception from the time of implantation".<sup>167</sup>

Thus, since many of the problems which are unique to IVF result  
from events occurring prior to implantation, current HEW  
regulations are of limited usefulness.<sup>168</sup>

#### B. State Laws

The only statutes which states have which, by analogy, are  
closest to the IVF area as those which deal with fetal research.  
At least fifteen states have such legislation, and virtually all  
of these statutes were passed within the two years following  
the Roe v. Wade decision.<sup>169</sup>

An analysis of state fetal research laws indicates a  
hodgepodge of regulation and prohibition, with little consistency  
among the various jurisdictions. For example, the South Dakota  
law states that experimentation with fetuses without written  
consent of the woman shall be prohibited.<sup>170</sup> No distinction is  
drawn between therapeutic and nontherapeutic research, or between  
in utero or ex utero research.

The Kentucky statutes states:



Whoever shall sell, transfer, distribute or give away any live or viable aborted child or permits such child to be used for any form of experimentation shall be imprisoned in the penitentiary for a term of not less than ten (10) nor more than twenty (20) years.<sup>171</sup>

This statute would penalize any person who consented to research on a fetus, although not the person who actually conducted the research. It does not apply to fetuses in utero, nor does it appear to permit therapeutic research.

Perhaps the most detailed statute is the Massachusetts one.<sup>172</sup> The statute begins by stating a general prohibition against all research on live human fetuses, whether before or after expulsion from the womb. The remainder of the statute lists exceptions to this general rule. One may study a fetus in utero if such a procedure does not "substantially jeopardize" the life or health of the fetus and provided the fetus is not the subject of a planned abortion. The mother is given the authority to consent to research on a dead fetus.<sup>173</sup>

An example of an extreme statute is that of Louisiana. Its law states that:

Human experimentation is the use of any live born human being, without the consent of that live born human being...for any scientific or laboratory research or any other kind of experimentation or study except to protect or preserve the life and health of said live born human being...<sup>174</sup>

The "crime of human experimentation" is punishable by imprisonment at hard labor for not less than five nor more than twenty years, or a fine of not more than ten thousand dollars, or both. This broad statute may be interpreted to outlaw all research on children, some institutionalized mentally ill persons, some

prisoners, and anyone else who cannot give consent for themselves since they are all "live born". In addition, any person who experiments on an individual who has not given adequate consent may be imprisoned for a long period of time. Beyond that, the term "consent" is not defined in the statute.

A similar problem, perhaps in an even more extreme form, exists in Maine, which outlaws the use of "any product of conception considered live born...for any form of experimentation", and subjects violators to a fine and imprisonment.<sup>175</sup> Since every person in existence is a "live born product of conception", this statute may ban all research on human beings in that state.

Other statutes deal with the issue in a nonuniform and haphazard manner. Utah seems to prohibit all in utero research, but says nothing about ex utero research. Ohio prohibits research on the "product of human conception which is aborted", but says nothing about in utero research.<sup>177</sup> Illinois outlaws the "exploitation or experimentation" of "aborted tissue".<sup>178</sup>

However, it is unlikely that any of these statutes have any effect on the IVF area, other than to regulate research with the implanted IVF conceptus, as is the case with the HEW fetal research regulations. None of the state laws were drawn with regulation of IVF research in mind, as the issue was not then before the state legislatures. The only way in which these laws could be applicable would be if, for this purpose, the term "fetus" or the related term used in a particular statute were interpreted to include an unimplanted IVF conceptus, and such an interpretation would be a highly unusual and strained construction of the statutory language.

C. Possible Restrictions on Government Regulation of IVF

There does not seem to be a constitutional right either to conduct research or to be a research subject.<sup>179</sup> In an analogous situation, the law will not permit an individual to consent to certain activities, such as his own murder, to a brawl, to a maiming, or to other activities which are regarded as a "breach of the peace" or a violation of "public policy". Thus, no one could consent to an experiment that was done in "such reckless, wanton or flagrant nature as to show utter disregard of the safety of others under circumstances likely to cause injury".<sup>180</sup> Accordingly, one who performs such an experiment is subject to criminal charges of mayhem, assault and battery, and manslaughter if the subject dies as a result.<sup>181</sup>

Not only is an individual's right to consent to danger circumscribed by existing criminal law, it is also relatively certain that the state could, if it so chose, make all or certain forms of dangerous human experimentation illegal. Such a statute would be based on the general proposition that "the interests of the public require such interference, and that the means are reasonably necessary for the accomplishment of the purpose, and not unduly oppressive upon individuals".<sup>182</sup>

For example, statutes making boxing subject to specific regulations do not violate the United States Constitution. In one case, such a statute was challenged by a fifty-one-year-old prize fighter who had fought in more than 300 bouts.<sup>183</sup> The court found that the athletic commission could rightfully conclude

that to allow him "to engage in such a contest would be to run the risk of serious injury to him".<sup>184</sup> The court went on to say that this risk "not a consideration purely personal to him", but that the state also had a legitimate interest in his health.<sup>185</sup> The court stated:

Two main purposes have prompted such legislation: First, the desire to prevent as far as possible certain brutal and degrading features which have in the past sometimes attended such contests, and, second to promote and protect such contests when conducted within the legitimate limits of a sport.<sup>186</sup>

By analogy, it may be concluded that any individual state, or the federal government, could regulate dangerous human experimentation to prevent reckless experiments and to promote and protect experimentation done according to specified rules.

If the state found, however, that certain types of experimentation were so dangerous that they could not be properly controlled, a statute to outlaw such experimentation altogether would probably also be valid. Thus, for example, certain statutes have outlawed the handling of snakes in religious ceremonies.<sup>187</sup> In accord with this view are the statutes of a majority of states which require riders of motorcycles to wear helmets under pain of criminal penalties. These statutes have almost universally been upheld on grounds similar to those used in the boxing and snake handling cases.<sup>188</sup>

Accordingly, the conclusion is that the government, either state or federal, may adopt laws limiting an individual's ability to conduct or participate in research, and may, under certain circumstances, proscribe dangerous or hazardous human experimentation altogether.<sup>189</sup> However, the constitutionality of any attempted



Of importance to this discussion are the Equal Protection Clause, which protects against arbitrary discrimination by the state, and the Due Process Clause, which protects against the state or federal deprivations of life, liberty, or property without due process.<sup>190</sup> These protections come in varying degrees. Any statute which impinges upon a "fundamental right" or involves a "suspect classification" will be subject to the "strict scrutiny" test.<sup>191</sup> In essence the burden will be on the state to show that the statute is necessary to protect a compelling state interest. There are two parts to this test. The state must establish a compelling interest which is advanced by the statute, which is a question of law for the courts. In addition, the state must show that the statute is necessary to advance its interest, and that there are no less restrictive alternatives. Under existing norms and case law, this burden of proof would be virtually impossible to satisfy.<sup>192</sup>

If, on the other hand, it is determined that no "fundamental interest" or "suspect classification" is involved, the plaintiff has the burden of showing that the statute is totally arbitrary. Thus, the statute will be upheld if the classification or statute is rationally related to a permissible state objective. The state has broad powers in this regard, termed "police powers", enabling it to enact legislation for the health and general welfare of its citizens. This test, called the "rational basis" test, is very easy for the state to meet.

For this reason it is important for the plaintiff to show that a "fundamental right" is involved. Exactly what constitutes

a "fundamental right" has been a source of continuing controversy. Basically, it is a matter for judicial interpretation and is therefore subject to change.

For example, in Prince v. Massachusetts,<sup>193</sup> the United States Supreme Court rejected a claim of deprivation of first amendment religious freedom, generally considered a "fundamental interest", and supported the interest of the state in protecting childrens' welfare under a statute prohibiting child labor. In so doing, the Court observed: "The right to practice religion freely does not include liberty to expose the community or the child to communicable diseases or the latter to ill health or death."<sup>194</sup> Similarly, in Jacobson v. Massachusetts,<sup>195</sup> the Court held that compulsory vaccination laws were reasonable regulations established to protect public health and safety, and therefore not in derogation of due process rights.<sup>196</sup>

In dealing with reproductive matters, the issue involves the right to marry,<sup>197</sup> the right of privacy,<sup>198</sup> as well as the right to procreate.<sup>199</sup> Modern cases support the proposition that marital and procreative decisions fall within a constitutionally-protected zone of privacy.<sup>200</sup> As long ago as 1941 the United States Supreme Court declared that man possesses the basic civil right to have offspring.<sup>201</sup> The Court in Griswold v. Connecticut<sup>202</sup> stated that the right to marital privacy was fundamental. The exact basis of its decision is unclear, however. Although the justices agreed on the result, they each reached the conclusion in a different way. In Eisenstadt v. Baird,<sup>203</sup> the Court struck down a statute prohibiting the dispensation of contraceptives to

single women as violative of a fundamental right of reproductive privacy.

The more recent case of Roe v. Wade<sup>204</sup> also spoke of a fundamental right to reproductive privacy. Such a right could be argued to include the right to reproduce by means of IVF. It is not certain, however, that the Court would extend Roe that far. In the case the Court weighed fetal versus maternal protection. It found that protection of the mother out weighed protection of the fetus during the early stages of pregnancy. However, this does not mean that the fetus, or in the case of IVF, the conceptus, is without protection.<sup>205</sup> If the state's interest in protecting the IVF conceptus out weighs the mother's privacy right in having an IVF child, governmental regulation of IVF would pass constitutional muster. There may be sufficient interest in preventing injury to a conceptus or fetus to warrant regulation of practice which may result in the birth of a defective child. Genetic intervention in individual cases may involve, to a greater extent than in the case of other medical procedures, important societal interests. The state would seem to have an important interest in regulating IVF because of the dangers and ethical issues raised by its use. Beyond that, since IVF experimentation occurs outside the woman's body, her right of privacy is less than that involved in abortion, and diminishes in comparison to the state's interest.<sup>206</sup> Thus, Roe should not present an overwhelming obstacle to governmental regulation of IVF.

There are also some other legal precedents which uphold government restrictions on reproductive rights, indicating that

societal interests may be sufficiently powerful to justify at least some regulation for limitations on reproduction.<sup>207</sup>

For example, in Buck v. Bell,<sup>208</sup> the Supreme Court upheld a Virginia statute providing for sterilization of inmates committed to state supported institutions who were found to have a "hereditary" form of insanity or imbecility.<sup>209</sup> Many states still have some form of compulsory sterilization legislation,<sup>210</sup> and courts typically uphold such statutes.<sup>211</sup>

Although this case was decided prior to those cases discussed alone which have increasingly recognized the right to have children as a fundamental right, the distinguishing features of Buck v. Bell do not indicate that the state cannot offer any compelling justifications to warrant mandatory restriction on reproduction. Such justification can be found in society's interest in safeguarding the health and welfare of its citizens, in the allocation of economic resources, and in population control.<sup>212</sup> In Buck v. Bell, Justice Holmes stressed that "it would be better for all the world...if society can prevent those who are manifestly unfit from continuing their kind".<sup>213</sup> Perhaps world conditions have become so complex and resources so valuable that society now has a compelling interest in restricting reproduction by those who, although not "manifestly unfit" themselves, perpetuate human suffering by giving birth to offspring who may be more likely to have genetic defects.

Thus, given the dangers of IVF research to the general welfare, it would seem that a compelling state interest can be effectively established for research control. It should be noted,



though, that if this societal interest is sufficient to sustain regulation of such actions, this would extend the arm of government regulation into an area of personal decision making where the need for intense privacy has heretofore been recognized.

However, once it is established that the state may use its police power to regulate an activity, the question of which level of government should administer the controls remains.<sup>214</sup> The matter could be subject to federal regulation, or it may be an appropriate concern for regulation by the police power of the states. Since research activities have national consequences, the need for uniformity of research controls should make federal action appropriate. The manipulation of IVF research through government funding policies seems to provide the most feasible method for regulation.

## VI. Conclusions and Recommendations

Significant hazards do exist, both to the individuals involved and to society as a whole, in undertaking IVF research and in application of the results of that research. With that in mind, and based on the foregoing analysis of the major legal issues in the area, I make the following conclusions and recommendations:

1. Appropriate, critical studies in primates and other animals must have been completed prior to undertaking IVF research, with the results indicating a scientific justification for proceeding onto tests with humans.

2. A review of the particular research protocol to determine its scientific merit must be undertaken, not only by the Ethical Advisory Board, but also by the Institutional Review Board at the specific research institution. This review should also take into account the qualifications of the IVF researchers, the available laboratory conditions, and the necessary safety standards for conducting the research.
3. Taking into account the present state of knowledge in the IVF area, and realizing that only humans can provide the test system for fully assessing the risks of using the procedure in humans, the risk at which the conceptus is placed must be the least possible consistent with successful completion of the research. However, if the objective of a particular experiment is to produce a live child, the risk to the conceptus must be minimal.
4. Recognizing that the mental state of a couple who desire to have a child by means of IVF may make obtaining truly informed consent difficult, it is nevertheless necessary to obtain informed consent, not only from the mother and the father, but also from any donor or "hostess" who may be involved in a particular incident.

5. While the consent obtained by the mother and father should include a provision whereby they each consent for the conceptus, an independent and objective guardian should nevertheless be appointed to represent the interests of the conceptus and to make the consent decision on its behalf. If the guardian, after reviewing the procedure, refuses to consent, that refusal should take precedence over the couple's consent decision, although it should still be open to court review in an action brought by either the researcher or the couple to determine whether the decision was "in the best interests" of the potential conceptus.
6. The entire consent process should be reviewed by the research institution's Institutional Review Board to determine its adequacy.
7. If a donor and/or "hostess" is involved in a particular IVF procedure, contracts should be drawn up and signed by the couple desiring the child and the other individual(s) detailing the rights, duties, and responsibilities of all parties concerned.
8. IVF research should be undertaken only to aid informed and consenting couples to have a child, or to obtain important medical information related to the reproduction process, genetic defects, or related areas, which information cannot be obtained by any other means.

9. Only as many eggs as are absolutely essential to ensure as much as possible the success of the procedure should be exposed to sperm and the possibility of fertilization. Only those fertilized eggs which, prior to implantation, are determined to be defective, or those which, following successful implantation of one fertilized egg from a group, are no longer essential to the completion of the procedure, may be destroyed.
10. Couples volunteering to participate in IVF experiment involving implantation with the objective of producing a live child should not be able to have a child by any other means so that IVF is the only viable option remaining to them.
11. No inducements, monetary or otherwise, should be offered to encourage any of the participants in the experiment.
12. A system for periodic review of the research should be developed and instituted at the individual research facility. If, during the course of such review, it is determined that there is more risk or harm to any involved party than originally anticipated, such as a definite increase in the number of infants born with genetic defects, a mechanism for immediate termination of the research must be available.



13. Following implantation of the IVF conceptus, the experiment is to be governed by the HEW fetal research regulations.
14. Following the birth of the IVF infant, any further research is to be governed by the HEW rules regulating experimentation with children.
15. A federal compensation scheme for those harmed as a result of IVF research should be developed and implemented.
16. There should be strong encouragement of states to pass appropriate statutes so as to resolve the present family law ambiguities in the IVF area.

Much of the current debate over the limits of IVF experimentation focuses on the issue of how much power society should exercise over scientific research decisions.<sup>215</sup> I am hopeful that my recommendations in this area have achieved a satisfactory balance between the need for continued scientific research in the area and the need for a legal and ethical standard of guidance.



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12. Plosowe, The Place of Law in Medico-Moral Problems: A Legal View II, 31 N.Y.U.L. Rev. 1238, 1242 (1956).
13. Hager, supra note 11, at 233.

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15. Smith, Through a Test Tube Darkly: Artificial Insemination and the Law, 67 Mich. L. Rev. 127, 135 (1968).
16. 49 Ont. L.R. at 22-23, 58 D.L.R. at 258.
17. Oakley, Test Tube Babies: Proposals For Legal Regulation of New Methods of Human Conception and Prenatal Development, 8 Family L.Q. 385, 386-87 (1974).
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19. Doornbos v. Doornbos, 23 U.S.L.W. 2308 (Super. Ct. Cook County, Ill., Dec. 13, 1954), appeal dismissed on procedural grounds, 12 Ill. App. 2d 473, 139 N.E.2d 844 (1956).
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31. 437 P.2d 495, 66 Cal. Rptr. 7 (1968).
32. Id. at 498, 66 Cal. Rptr. at 10.
33. Id. at 498-500, 66 Cal. Rptr. at 10-12.
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63. Jacobs v. Theimer, 519 S.W.2d 846 (Tex. 1975)
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103. See generally G. Annas, L. Glantz & B. Katz, supra note 100.
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171. Kentucky Rev. St. 436.026.
172. Mass. Gen. Laws Ch. 112, § 12J.
173. See Culliton, Fetal Research: The Case History of a Massachusetts Law, 187 Sci. 237 (1975); Culliton, Fetal Research (II): The Nature of a Massachusetts Law, 187 Sci. 411 (1975).
174. La. Rev. St. Title 14, § 87.2.
175. Maine Rev. Statutes Title 22, § 1574.

176. Utah Crim. Code 76-7-316.
177. 1974 Laws of Ohio, Am. Sub. House Bill 989.
178. Ill. Crim. Law and Proc. Ch. 38, § 81-18.
179. See G. Annas, L. Glantz & B. Katz, supra note 100, at 50-53.
180. See Banovitch v. Commonwealth, 196 Va. 210, 83 S.E.2d 369 (1954).
181. Id. See State v. Fransua, 85 N.M. 173, 510 P.2d 106 (Ct. App. 1973).
182. Lawton v. Steele, 152 U.S. 133, 137 (1894). And see Goldblatt v. Hempstead, 369 U.S. 590, 594 (1962).
183. Fitzsimmons v. New York State Athletic Commission, 146 N.Y. Supp. 117 (1914), aff'd without opinion, 147 N.Y. Supp. 1111 (1914).
184. Id. at 122.
185. Id.
186. Id. at 120.
187. See Tennessee v. Pack, 527 S.W.2d 99 (Tenn. 1975).
188. E.g., People v. Newhouse, 55 Misc. 2d 1064, 287 N.Y.S.2d 713 (1968); State v. Mele, 247 A.2d 176 (N.J. 1968); State v. Odegaard, 165 N.W.2d 667 (N.D. 1969); Bisenius v. Karns, 42 Wisc. 2d 42, 165 N.W.2d 377 (1969). Contra, American Motorcycle Ass'n v. Davids, 11 Mich. App. 351, 158 N.W.2d 72 (1968).
189. G. Annas, L. Glantz & B. Katz, supra note 100, at 53.
190. See Kinney, supra note 10, at 516-17.
191. See, e.g., Dandridge v. Williams, 397 U.S. 471 (1970); Shapiro v. Thompson, 394 U.S. 618 (1969).
192. Note, Governmental Control of Research in Positive Eugenics, 7 J. Law Ref. 615, 620 (1974).
193. 321 U.S. 158 (1944). In that case, children of Jehovah's Witnesses had been working in violation of state child labor laws.
194. Id. at 166-67.
195. 197 U.S. 11 (1905).
196. Id. at 25.
197. Loving v. Virginia, 388 U.S. 1 (1967).
198. Griswold v. Connecticut, 381 U.S. 479 (1965).

199. Skinner v. Oklahoma, 316 U.S. 535 (1941).
200. See, e.g., Eisenstadt v. Baird, 405 U.S. 438, 452-55 (1972). See also Smith, Manipulating the Genetic Code: Jurisprudential Conundrums, 64 Georgetown L.J. 697, 705-07 (1976).
201. Skinner v. Oklahoma, 316 U.S. 535, 541 (1941).
202. 381 U.S. 479, 495 (1965).
203. 405 U.S. 438 (1972).
204. 410 U.S. 113 (1973).
205. See Note, supra note 54; Green, Genetic Technology: Law and Policy for the Brave New World, 48 Indiana L.J. 559, 565 (1973). See generally Wilson, Fetal Experimentation: Rights of the Father and Questions of Personhood, 22 Villanova L. Rev. 403 (1976-77).
206. See Kass, supra noted 3, at 32-33.
207. See Golding & Golding, Ethical and Value Issues in Population Limitation and Distribution in the United States, 24 Vand. L. Rev. 495, 512 (1971).
208. 274 U.S. 200 (1927).
209. Id. at 207.
210. See Pate & Plantz, Sterilization of Mental Defectives, 3 Cumberland-Samford L. Rev. 458 (1972).
211. E.g., In re Moore, 221 S.E.2d 307(N.C. 1976).
212. See Virkowich, The Dawning of the Brave New World - Legal, Ethical and Social Issues of Eugenics, 1971 U. Ill. L.F. 189, 203.
213. 274 U.S. at 207.
214. See Note, supra note 192, at 630-31.
215. See generally Balmer, Recombinant DNA: Legal Responses to a New Biohazard, 7 Environ. L. 293 (1977); Delgado & Millen, God, Galileo, and Government: Toward Constitutional Protection For Scientific Inquiry, 53 Wash. L. Rev. 349 (1978); Graham, Concerns About Science and Attempts to Regulate Inquiry, Daedalus 1 (Spring 1978); Swazey, Protecting the "Animal of Necessity": Limits to Inquiry in Clinical Investigation, Daedalus 129 (Spring 1978); Note, Recombinant DNA and Technology Assessments, 11 Ga. L. Rev. 785 (1977).



LEGAL CONTROL ON USE OF HUMAN TISSUE IN EXPERIMENTATION

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## I. Introduction

This paper is a survey of laws and regulations governing the use of human tissue for experimental purposes. The focus will be upon the review procedures which deal with the researcher's use of the tissue and the consent he must obtain for that use. There are three sources from which human tissues may be obtained and used for experimental purposes: (1) autopsies and donations, (2) fetal tissue obtained as a result of spontaneous or induced abortions, and (3) tissue discarded following surgery or routine diagnostic procedures.

Briefly, local state statutes govern autopsies, donations and fetal tissue; while Federal DHEW regulations deal with all tissue use, excluding fetal material. However, with respect to the DHEW regulations, there are problems associated with the actual procedures used to obtain consent, and with the institutional review of the tissue use.

## II. State Law Materials

### A. Autopsy and Donation

In the words of its drafters, the Uniform Anatomical Gift Act (UAGA) was drawn up in order to "encourage the making of anatomical gifts" and to eliminate "uncertainty as to the applicable law" and

<sup>1</sup>  
 protect all concerned parties. The UAGA has been adopted in all  
 fifty states and the District of Columbia, with minor changes which  
<sup>2</sup>  
 are not relevant for the purposes of this survey. "Any individual  
 of sound mind and eighteen years of age or more" is allowed to donate  
<sup>3</sup>  
 all or part of his body, "the gift to take effect upon death." If  
 the decedent himself has not made arrangements for such disposition  
 of his body, the UAGA sets forth a priority listing of other persons  
 who may make the gift, in the following order: the spouse, an adult  
 son or daughter, either parent, an adult brother or sister, a guar-  
 dian of the decedent at his death, or any other person authorized to  
<sup>4</sup>  
 dispose of the body. Actual notice to the donee of opposition to the  
 gift by the decedent or a person in a prior class or the same class as  
<sup>5</sup>  
 the donor, will preclude the donee from accepting the gift. Donees  
 may be hospitals, physicians, medical schools, organ banks, or  
<sup>6</sup>  
 similar enumerated institutions.

The donation may be testamentary; that is, made by the  
 decedent by his will. The gift will be effective without going  
<sup>7</sup>  
 through probate, even if the will itself is invalid. For a non-  
 testamentary gift, the UAGA contains two suggested donation forms,  
 one for use by a living donor, the other for donation by one of the  
<sup>8</sup>  
 other authorized persons. Variations on these forms have been  
 adopted by the states, the most common being linked in some way with  
<sup>9</sup>  
 an individual's driver's license.



A second group of statutes is concerned with autopsies and post-mortem examinations. A wide variation exists among the states as to who may perform an autopsy, ranging from restricting<sup>10</sup> the right to physicians only, to allowing residents, interns,<sup>11</sup> and supervised medical students to perform the operation. In the absence of permission prior to the decedent's death, a priority<sup>12</sup> system similar to that of the UAGA is generally used, usually<sup>13</sup> with provision being made for obtaining a valid consent via telephone.

Other acts also provide for the use of unclaimed bodies of paupers and indigents for the advancement of medical science.<sup>14</sup> Statutes which are concerned with forensic medicine and medical examiner-initiated autopsies are not relevant to our discussion, since the remains would revert to the decedent's estate for final disposition by way of the UAGA.

The actual consent forms used by hospitals tend on their face to follow the statutory dichotomy between anatomical gifts and post-mortem examinations, but there is an interesting overlap. For example, in Boston, University Hospital uses different consent forms<sup>15</sup> for anatomical gifts and post-mortem examinations. For an anatomical gift, three copies of the consent form are used, one each for the donor, the anatomy department and medical records. Boston University Medical Center, consisting *inter alia* of a teaching hospital and a medical school, is named as the donee "for the purposes of education, research, therapy, and/or the advancement of medical science." The entire body or specified organs may be donated, and B.U.M.C. is allowed to transfer the gift to another donee, one authorized under

the law. If the entire body is donated, the remains after use are to be either released to the decedent's estate, or buried by B.U.M.C. in a named cemetery, with a religious service of the donor's choice. Pursuant to the state statute, the signatures of two witnesses are required, in addition to that of the donor.

Instructions are stapled to the consent forms for use by the hospital staff. The donor priority listing is provided, along with an explanation of objection rights. The instructions suggest that one of the witnesses be a "unit secretary," and, if the whole body is to be donated, a copy of a booklet entitled "Human Anatomy and Medical Education" is made available to the donor.

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For a post-mortem examination, a different form is used. This form is extremely similar to the one utilized by the National Institutes of Health.<sup>18</sup> It permits University Hospital to perform a post-mortem, and allows "removal or retention for use for scientific or therapeutic purposes of such organs and tissues as the physicians and surgeons in attendance at University Hospital may deem necessary." A blank line is then provided in order to add any restrictions on this broad consent. Consent via telephone is allowed, and mention is made that nurses should not be used as witnesses. Again, the statutory priority listing and explanation is provided.

The Massachusetts General Hospital and the Sidney Farber Cancer Center use similar post-mortem forms.<sup>19</sup> However, theirs

state that tissue and organs may be removed for grafting or transplantation.

These post-mortem consent forms allow the hospital to exercise much greater leeway in the way they obtain materials. There is, for example, no provision for dealing with opposition by persons in higher priority classes. Little or no explanation is made to the donor, before or after the autopsy. No mention is made of final disposition of the removed tissue, other than that the institution is entitled to retain it;<sup>20</sup> and, apparently, the responsibility for burial of the body rests with the estate. The post-mortem consent forms are worded in a way that avoids the more precise procedural provisions of the UAGA. The institution is allowed to take what it desires and is not limited to what is specifically donated.

Institutional review of the uses of autopsy materials and donor consent will be discussed below in Section III.

#### B. Fetal Tissue

The second source of human tissue for experimentation purposes is fetal tissue obtained from spontaneous or induced abortions. The UAGA is applicable to this source as well, since a "decedent" is defined in the Act as "a deceased individual and includes a stillborn infant or fetus."<sup>21</sup> The donor under the Act could, of course, be "either parent."<sup>22</sup> One parent should be able to prevent such a donation by the other,<sup>23</sup> but actual notice to the donee is required, and the donee is under no duty to inquire.<sup>24</sup>

Apart from the UAGA, there are only six states which have enacted statutes dealing with the use of tissue from an aborted fetus.

The Ohio statute reads:

(A) No person shall experiment upon or sell the product of human conception which is aborted. Experiment does not include autopsies pursuant to sections 313.13 and 2108.50 of the Revised Code.<sup>26</sup>

Illinois only allows an analysis and tissue report by a pathologist and states "there shall be no exploitations of or experi-<sup>27</sup>mentation with the aborted tissue." Similarly, Indiana prohibits all experiments except a pathological examination and does not allow<sup>28</sup> transportation out of state of the fetus for experimentation.

South Dakota simply requires written consent of the mother<sup>29</sup> for experimentation.

<sup>30</sup>Massachusetts and <sup>31</sup>North Dakota have identically worded statutes: "No experimentation may knowingly be performed upon a dead fetus unless the consent of the mother has first been obtained, provided, however, that such consent shall not be required in the case of a routine pathological study."

In his study for the National Commission for the Protection of Human Subjects of Biological and Behavioral Research, Professor A.M. Capron states that: "The net effect of these two laws [South Dakota and Massachusetts] would seem simply to be that the father of



the fetus is deprived of the authority (granted under the UAGA) to be the sole person consenting to the use of that fetus after death . . . ."

Professor Capron continues:

It should be noted that all of these provisions, to the extent that they modify the UAGA rules on experimentation with dead fetuses and the like, apply only to the products of induced and not spontaneous abortions. Although the language in them is broader, this must be read in the context of anti-abortion statutes . . . .<sup>32</sup>

The only other laws which might apply are grave-robbing statutes. However, there has been only one indictment under such a law. In 1974, four Boston physicians were prosecuted under the Massachusetts grave-robbing law. They had obtained the consent of pregnant women seeking abortions to participate in an experiment, but had neglected to get consent to study the fetuses after the  
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abortion.

With respect to live fetuses, it should be noted that eight states prohibit experimentation on live fetuses, with criminal penalties associated with violations.<sup>34</sup> The Massachusetts and North Dakota statutes discussed above prohibit experimentation on a live fetus, although procedures are allowed which study the fetus, provided the fetus is not jeopardized and it was not obtained through an abortion.<sup>35</sup>

A consent form used by a Boston hospital for the termination of pregnancy includes, as part of it, consent for experimental use of

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the fetal materials. The form authorizes the hospital "to dispose of any tissue, or parts, or organs which may be removed." Continuing, the subject states, "I further consent for fetal and placental tissues from this pregnancy to be used in scientific research in accordance with the Laws of Massachusetts. I understand that this consent authorizes the transfer of these products of conception for the above purposes." The mother's refusal to consent is accomplished by crossing out these statements.

### C. Discarded Tissue

There are no statutes which deal with the use for research purposes of human tissue discarded after surgical or diagnostic procedures. This is one area in which the states have not spoken. However, the United States Department of Health, Education and Welfare (DHEW) has established administrative rules which are relevant to this source of tissue (see Section III, below).

### III. Federal Statutes and Regulations

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The National Research Act of 1975 amended the Public Health Service Act by requiring the Secretary of Health, Education and Welfare to promulgate regulations for the protection of human subjects of re-

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search. These regulations, codified in 45 C.F.R. 46, are applicable

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to all institutions receiving DHEW funds. As we shall see, they speak to all three areas of research considered in this survey.

Section 46.102 sets out the policy considerations behind the regulations. In order to safeguard the rights and welfare of research subjects, DHEW requires an Institutional Review Board (IRB) at each facility to certify to DHEW that they have reviewed and approved each research project for conformity with DHEW regulations.<sup>40</sup> The review is to determine whether subjects will be at risk, and, if so, whether:

(1) The risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept these risks;

(2) The rights and welfare of any such subjects will be adequately protected; and

(3) Legally effective informed consent will be obtained by adequate and appropriate methods in accordance with the provisions of this part.<sup>41</sup>

"Subject at risk" is defined as:

[A]ny individual who may be exposed to the possibility of injury, including physical, psychological or social injury, as a consequence of participation as a subject in any research, development, or related activity which departs from the application of those established and accepted methods necessary to meet his needs, or which increases the ordinary risks of daily life, including the recognized risks inherent in a chosen occupation or field of service.<sup>42</sup>

The Institutional Guide to DHEW Policy on Protection of Human Subjects (henceforth, "Guide") elaborated on the Regulations.

An individual who may be at risk can include, "patients; outpatients; *donors or organs, tissues, and services,*" and "the unborn and the dead should be considered subjects to the extent that they have rights which can be exercised by their next of kin or legally authorized representatives." <sup>43</sup> The Guide goes on to state:

There are also medical and biomedical projects concerned solely with organs, tissues, body fluids, and other materials obtained in the course of the routine performance of medical services such as diagnosis, treatment and care, or at autopsy. The use of these materials obviously involves no element of physical risk to the subject. *However, their use for many research, training, and service purposes may present psychological, sociological, or legal risks to the subject or his authorized representatives.* In these instances, application of *the policy requires review* to determine that the circumstances under which the materials were procured were *appropriate* and that *adequate and appropriate consent was, or can be, obtained* for the use of these materials for project purposes.<sup>44</sup>

Under the terms of the regulations and Guide, all use of human tissue for experimental purposes is considered as experimentation, and must be reviewed by the IRB. However, informed consent by the subject or a subject's representative is required only when the subject is "at risk." Administrative staff may separate projects which involve animal or non-human materials from those which involve human materials. But, with respect to the use of human tissue, "determinations as to whether any project or activity involves human subjects at risk is a professional responsibility to be discharged through review by the



committee, or by subcommittee." Current National Institutes of Health policy is to require a *written* protocol for "procedures previously generally accepted as being essentially without risk in this Institution including collection of blood, urine, and tissue. Similarly, research involving removal of or the use of removed organs, tissue(s), fluids, and other materials from human subjects must also be written in protocol form for review and approval." 46

When the determination is made that the subject is at risk, informed consent is required by the regulations. The regulations are silent as to the need for informed consent where the subject is determined not to be at risk. Obviously, it would seem that internal institutional procedures for defining "at risk" have significant legal implications.

DHEW regulations specify the following definition of "informed consent":

[T]he knowing consent of an individual or his legally authorized representative, so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion. The basic elements of information necessary to such consent include:

- (1) A fair explanation of the procedures to be followed, and their purposes, including identification of any procedures which are experimental;
- (2) A description of any attendant discomforts and risks reasonably to be expected;
- (3) A description of any benefits reasonably to be expected;

(4) A disclosure of any appropriate alternative procedures that might be advantageous for the subject;

(5) An offer to answer any inquiries concerning the procedures; and

(6) An instruction that the person is free to withdraw his consent and to discontinue participation in the project or activity at any time without prejudice to the subject.<sup>47</sup>

Furthermore, exculpatory language waiving the subject's rights or releasing the institution from liability may not be included within  
48  
the obtained consent.

Three ways of documenting the consent are allowed. First is a written document containing all of the elements described above signed by the subject. It may be read to the subject, but he must  
49  
read it himself nonetheless (or his representative may do so). Second is a so-called "short form" stating that the elements of informed consent "have been presented orally to the subject . . . ." Summaries  
50  
of the oral presentation must be retained by the IRB. Under the third form, the IRB may modify either of the first two procedures. However,

Granting of permission to use modified procedures imposes additional responsibility upon the Board and the institution to establish: (1) that the risk to any subject is *minimal*, (2) that use of either of the primary procedures for obtaining informed consent would *surely invalidate objectives of considerable immediate importance*, and (3) that any reasonable alternative means for attaining these objectives would be *less advantageous to the subjects*. The Board's reasons for permitting the use of modified procedures must be individually and specifically documented. . . .<sup>51</sup>

To summarize, the DHEW regulations contained in 45 C.F.R. 46 govern use of human tissues for research or experimental purposes, including tissue obtained from autopsy or discarded following surgical or diagnostic procedures. Research on material from a dead fetus is not governed by the regulations, but only by state law. IRB review of written protocols detailing the research is required. No exceptions are provided for use of autopsy or discarded material. Where the subject providing the tissue is "at risk," informed consent is required. The IRB is responsible for determining if the subject is "at risk," and for reviewing the validity of the consent.

It should be noted that the regulations serve in effect as guidelines because of the difficulty of enforcing compliance with their provisions. Generally, DHEW possesses neither adequate funding nor staff to monitor the research institutions. The FDA is only now attempting such a procedure for New Drug Investigations. Technically, research funds to a non-complying institution may be cut off if non-compliance were found, but it is more likely that efforts at corrective action would be encouraged in lieu of the more severe remedy.

A description of the practices followed by teaching hospitals in the Boston area (a national center of medical treatment and research) in the use of autopsy and discarded materials, indicates a range of procedures establishing formal compliance with the DHEW regulations.

1. Boston University Medical Center:

No consent is required to be obtained for the use in research of tissues discarded following routine clinical use. However, "investigators [researchers] will communicate to the chairman of the committee [IRB] their intent to use tissues for various purposes, specifying the purposes for which they will be used, the amount to be used, as well as the source from which they will obtain these materials." The committee reviews the submission, and responds in writing. "It is further understood that the use of these biological materials by investigators will in no way pose a threat to the donor's right of privacy, nor is there any involvement of risk for the individuals from whom the biological materials are obtained." 57

2. Tufts -- New England Medical Center:

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Basically uses the same procedure as BUMC.

3. Harvard Medical School:

Review is made of all research. Written protocols must be submitted to the Human Studies Committee [an IRB]. 59

- a. Massachusetts General Hospital: All research activities are reviewed, and consent is required. "By the agreement on the part of the subcommittee to be responsible for the performance of certain types of studies, i.e., studies involving such



things as the removal of small amounts of venous blood, the examination of excreta, or certain types of psychological tests. In these instances the subcommittee may agree that oral consent on the part of a subject is all that will be required." 60

b. Boston Hospital for Women: If subjects are at risk, a complete protocol, and the most comprehensive of the three DHEW consent forms allowed, 61 must be submitted to the IRB.

c. Children's Hospital Medical Center: No review is made unless the research receives DHEW funding. If so, the requisite forms are marked that tissue from autopsies or discarded tissue is involved, and no subject is at risk. Reportedly this procedure has been approved by NIH, and is followed for reasons of administrative efficiency. 62

d. Beth Israel Hospital: Written protocols were used in the past, but now the entire process 63 appears to be done orally.

4. Lahey Clinic (not a teaching hospital):

"Where the study involves the use of blood samples or therapeutic procedures and the risk of the diagnostic or therapeutic procedure is not altered significantly by the study, no permission or informed consent will be required." Protocols must be submitted for all research. If there is a likelihood that anonymity of a subject may be jeopardized, informed consent (following the DHEW regulations) may be required.<sup>64</sup>

IV. Professional Codes

The only applicable standards are the Nuremberg Code,<sup>65</sup>  
the Declaration of Helsinki,<sup>66</sup> and the A.M.A. Principles of Medical  
Ethics.<sup>67</sup> All are extremely general guidelines setting forth the proper ethical position for a physician conducting clinical research.

FOOTNOTES

1. U.A.G.A., Commissioner's Prefatory Note.
2. For citations and discussion, see *Hospital Law Manual*, Attorney's Volume, Volume II.
3. U.A.G.A. § 2.
4. U.A.G.A. §§ 2 (b) 1 to 2 (b) 6.
5. U.A.G.A. § 2 (c).
6. U.A.G.A. § 3.
7. U.A.G.A. § 4 (a).
8. U.A.G.A. § 4, Commissioner's Note.
9. E.g., Mass. Gen. Laws Ann., ch. 90, § 8 (1971); see note 2 above.
10. E.g., Mich. Stat. Ann. § 14.524 (1969); see note 2 above.
11. E.g., N.Y. Public Health Law § 4209 (1971); see note 2 above.
12. E.g., Va. Code Ann. § 32-364.4:1 (Supp. 1975); see note 2 above.
13. E.g., Pa. Stat. Ann. tit. 35, § 1112 (1964); see note 2 above.
14. E.g., N.J. Stat. Ann. §§ 45:9-43 to 45:9-55 (1963); see note 2 above.
15. See Appendix B., Courtesy of Edward J. Christiansen, Jr., Esq. (Counsel U.H
16. See Appendix C.
17. See Appendix D.
18. The NIH form authorizes "the removal and retention or use for diagnostic, scientific, or therapeutic purposes [of] any parts, tissue or organs as such physicians or their designees may deem proper . . . ." Letter and enclosure from Michael A. Lopatin, Chief, Medical Board Services, the Clinical Center, NIH, Sept. 27, 1978. See Appendix H.

19. See Appendix E.
20. Where retention is not mentioned, see *Hendriksen v. Roosevelt Hospital*, 297 F. Supp. 1142 (N.Y. 1969); *Palmquist v. Standard Accident Insurance Co.*, 3 F. Supp. 358 (S.D. Cal. 1933); *Hassard v. Lehane*, 143 App. Div. 424, 128 N.Y. Supp. 161 (1911); accord, *Bonilla v. Reeves*, 267 N.Y.S. 2d 374 (1966).
21. U.A.G.A. § 1 (b).
22. U.A.G.A. § 2 (b) 3.
23. U.A.G.A. § 2 (b).
24. U.A.G.A. § 2 (c).
25. Note; New Mexico H.B. Nos. 441, 442 (Laws 1977) authorizes the Board of Medical Examiners to regulate or prohibit experimentation on aborted fetuses having one or more vital life signs at the time of abortion. Copies of the law and administrative interpretation are not available at this time.
26. Ohio Rev. Code Ann. tit. 29 § 2919.14 (1975).
27. Ill. Ann. Stat. ch. 38 § 81-8 (Smith-Hurd 1977).
28. Ind. Code Ann. § 10-112 (Supp. 1975).
29. S.D. Compiled Laws Ann. § 34-23A-17 (Supp. 1976).
30. Mass. Gen. Laws Ann. ch. 112 § 12J (Supp. 1978).
31. N.D. Cent. Code § 14.02.2-02 (Supp. 1977).
32. A.M. Capron, "The Law Relating to Experimentation with the Fetus," Appendix to the National Commission for the Protection of Human Subjects of Biological and Behavioral Research report on *Research on the Fetus*, DHEW Publ. No. (OS) 76-128, p. 13-7.
33. See, Culliton, "Grave Robbing: The Charge Against Four from Boston City Hospital," *Science* 186:420, 1974.
34. Ky. Rev. Stat. § 436.026 (1975); La. Rev. Stat. Ann. § 14:87.2 (1974); Me. Rev. Stat. Ann. tit. 22, § 1593 (Supp. 1978); Minn. Stat. Ann. §§ 145.421, 145.422 (Supp. 1978); Mo. Ann. Stat. § 188.035 (Supp. 1978); Mont. Rev. Codes Ann. § 94-5-617 (Supp. 1977); Neb. Rev. Stat. § 28-4, 161 (1975); Pa. Stat. Ann. tit. 35, § 6605 (1977); see also, Cal. Health & Safety Code § 25956 (Supp. 1978).



35. See Notes 30 and 31 above.
36. See Appendix F.
37. 42 U.S.C. 747 (a), (NRA)., 42 U.S.C. 2891 (PHSA).
38. Changes to the basic regulations have been proposed after recommendations by the National Commission for the Protection of Human Subjects of Biological and Behavioral Research. Currently under review are rules pertaining to children (see, 43 Fed. Reg. 2084 (1978)), the mentally infirm (see, 43 Fed. Reg. 11329 (1978)), and prisoners (see, DHEW Publ. No. (OS) 76-131).
39. See Appendix G-i. It is expected that regulations of the Secretary issued pursuant to this authority will eventually serve as a model for uniform rules for all Federal agencies. Currently, however, they apply only to research funded through the constituent agencies of DHEW. They have, however, served as models for the Energy Research and Development Administration and the Consumer Product Safety Commission. See, 10 CFR 745; 41 Fed. Reg. 3710 (1976). Regulations governing experimentation undertaken by the Armed Forces are similar to those adopted by DHEW. See, United States Army Medical Research and Development Command Regulation, 70-25 (Oct. 8, 1975); Naval Medical Research and Development Command Notice 3900 (Nov. 3, 1975); Air Force Regulation 169-8 (Aug. 19, 1974).
40. 45 C.F.R. § 46.102 (a). For an in-depth discussion of the certification and assurances to DHEW, see the copy of the regulations in their entirety, in Appendix G.
41. 45 C.F.R. §§ 46.102 (b) 1 to 46.102 (b) 3.
42. 45 C.F.R. § 46.103 (b).
43. "The Institutional Guide to DHEW Policy on Protection of Human Subjects," DHEW Publ. No. (NIH) 72-102, p. 2. (This publication is now obsolete; however, the policies embodied within it are still valid today. Privacy protections are the most important criteria used by NIH. See, note 53 below, and Appendix G-ii). 45 C.F.R. § 46.210 defers to state law regarding research with material from a dead fetus. This allows the state requirements for consent, or prohibitions on experimentation, to be effective. See II, B, above.

44. "Guide," p. 3. Emphasis added.
45. *Ibid.*, p. 5. "Committee" means the IRB.
46. See Appendix H. (Note 18 above).
47. 45 C.F.R. § 46.103 (c).
48. 45 C.F.R. § 46.109.
49. 45 C.F.R. § 46.110 (a).
50. 45 C.F.R. § 46.110 (b).
51. 45 C.F.R. § 46.110 (c). Emphasis added.
52. Form HEW-596 must be submitted to DHEW with the reviewed protocol. See Appendix I.
53. Telephone conversations with Dr. Robert C. Backus, Office for Protection from Research Risks, NIH (Sept. 27, 1978 and Oct. 11, 1978) confirmed this policy. The *only* exceptions are for "old" tissue cultures, and if there is no identification of, or possibility of identifying, subjects. However, this position raises some questions since, on the one hand, identification can be "lost" and, on the other, there appear to be tissue cultures which are identified, such as the "HeLa" strain.
54. 43 Fed. Reg. 35186 (1978).
55. 45 C.F.R. § 46.121.
56. See note 53 above.
57. Letter to NIH, courtesy of Mrs. Elisabeth Williams, IRB Staff, B.U.M.C. For full text of letter and sample protocol with reply, see Appendix J.
58. Telephone conversation with Sherwood L. Gorbach, M.D., Chairman of IRB, Tufts-New England Medical Center, Sept. 26, 1978.
59. "Policies and Procedures of the Harvard Committee on Human Studies," 1974. See Appendix K.

60. "Format for Review of Activities Involving Human Subjects that are the Responsibility of the Committee on Research," courtesy of Edgar B. Taft, M.D., IRB Staff, M.G.H. See Appendix L.
61. "Application for Approval of Investigation Involving Human Subjects," courtesy of Mr. Stanley Burchfield, IRB Staff, B.H.W. See Appendix M. It is unclear what consent is required for the use of discarded tissue.
62. Telephone conversation with Ms. Gwen O'Sullivan, IRB Staff, C.H.M.C., Sept. 26, 1978.
63. Telephone conversation with Leonard Bushnell, M.D., IRB Chairman, B.I.H., Sept. 26, 1978.
64. "Policies and Procedures Manual for Clinical Investigation," courtesy of Elton Watkins, Jr., M.D., Division of Research, Lahey Clinic Foundation. See Appendix N.
65. See Appendix O.
66. See Appendix P.
67. See Appendix Q.





21

PUBLIC OPINION SURVEY

BY

THE GALLUP POLL

AUGUST, 1978

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## NOTE TO READER

**The Sample:** The sampling procedure of the Gallup Poll is designed to produce samples which are representative of the U.S. civilian adult population. National survey results are based on interviews with a minimum of 1,500 adults.

**Sampling Tolerances:** In interpreting survey results, it should be remembered all sample surveys are subject to sampling error, that is, the extent to which the results may differ from what would be obtained if the whole population had been interviewed. Samples of 1,500 have a tolerance within 3 percentage points 95 percent of the time. Certain population groups are not reported separately for many surveys because the number of persons in the sample is not enough to provide sufficiently accurate results.

**Survey Dates:** The dates used in this report are the dates when the field work was done; generally one and one half or two weeks prior to publication dates. For some topics—those where the time factor is unimportant—interviewing dates are often more than two weeks prior to publication.

# *Most Americans support and would undergo the vitro-fertilization process*

If the federal government decides to fund vitro-fertilization research—the process of uniting a human sperm and an egg outside a woman's body—the decision would meet with the approval of most Americans.

While the government is trying to decide whether this kind of research should be federally funded, the Gallup Poll, in a survey conducted after the birth of the successful "test tube baby" last July, found the public favorably disposed toward this procedure.

Specifically, the survey found the following:

- \* An extraordinary 93 percent had heard or read about the baby, a girl born in England;
- \* Among those who had heard or read about the birth, understanding of this relatively complicated process was high;
- \* By a two-to-one margin, the public approved of the procedure;
- \* A majority of Americans said they would be willing to undergo this procedure if they were childless, wanted to have a child, and this would allow them to do so.

The birth of Louise Brown and the procedure by which she was conceived—the vitro-fertilization process whereby one of her mother's eggs and her father's sperm were united in a laboratory dish and then implanted in her mother's womb—clearly fascinated many Americans.

An extraordinarily large segment of the public, 93 percent, had either heard or read about the baby's birth. In no group of Americans did this familiarity fall below 79 percent and among some groups it reached as high as 98 percent.

But the public's interest in the birth goes well beyond just knowing it happened.

Of those who had heard or read about the birth four in 10 (42 percent) were also able to explain exactly what happened—that an egg was taken from the mother's body and fertilized with the father's sperm in a culture medium and then reimplanted in the mother's womb.



Predictably, understanding of the process was highest among the so-called upscale socio-economic groups—that is, those in the upper education and income brackets and those who work in either business or the professions—and lowest in the downscale groups.

## UNDERSTANDING IS KEY

Provided an explanation of the operation, the public is favorably disposed to its use.

By a two-to-one margin, Americans favor the use of this procedure and operation to aid childless couples. While 60 percent of all Americans said they favored the operation, about half as many, 27 percent, opposed it and 13 percent were undecided.

Clearly, understanding of the procedure is a key in the formation of these attitudes. For example, support for the operation was generally highest among those groups most likely to have heard or read about the procedure and who were best able to explain what takes place—that is, the upscale or “better off” segments of society. In fact, among people who fully understand the procedure, approval of the operation reached 75 percent.

Generally, the same pattern of opinion obtained when people were asked whether they would be willing to undergo the procedure if they were unable to have a child, wanted one, and this procedure would allow them to conceive.

About half the public, 53 percent, said they would undergo this procedure while 36 percent would not and 11 percent were undecided.

Interestingly, men and women had about the same views on both these questions. And, despite the Roman Catholic church’s labeling of vitro-fertilization as “illicit,” Catholics were favorably disposed toward the operation (56 percent) and half (50 percent) said they would use this route to conceive if they had to.

This is not to say, however, that conventional religious beliefs have no effect on attitudes as regards the operation and willingness to have it performed in an otherwise hopeless situation.

As regards attitudes toward the operation per se, church attenders—those who profess to have attended church in the week prior to the survey—favored the operation by a 51–35 percent margin while non-attenders came down on the same side of the question, but by a much wider 65–23 percent count.

In their willingness to undergo the operation should the circumstances demand it, church attenders were split in their feelings, with 44 percent saying they would be willing to use the procedure and 44 percent unwilling. Among non-attenders opinion split 59–31 percent in favor of using the procedure.

# FAMILIARITY WITH "TEST TUBE BABY" OPERATION

Question: "Have you heard or read about the baby born in England from an egg fertilized outside her mother's body?"

(Those who had heard about the operation were then asked the following question.) "Just as you understand it, how was this done?"

August 4 - 7, 1978

	Percent heard or read of operation	BASED ON THOSE WHO HEARD OR READ			
		Full, correct explanation	Partial, correct explanation	Mis- cellaneous	Don't know
NATIONAL	93%	42%	19%	15%	24%
SEX					
Male	94	41	21	15	23
Female	93	43	18	14	25
RACE					
White	95	44	19	15	22
Non-White	79	18	18	16	48
EDUCATION					
College	97	55	20	12	13
High School	95	41	20	16	23
Grade School	82	18	9	21	52
REGION					
East	98	44	19	18	19
Midwest	93	41	18	13	28
South	89	38	20	13	29
West	95	47	20	13	20
AGE					
Total under 30	95	43	21	17	19
18 - 24 years	95	40	23	15	22
25 - 29 years	95	48	19	17	16
30 - 49 years	95	47	20	11	22
50 & older	91	37	17	16	30
INCOME					
\$20,000 & over	98	55	18	15	12
\$15,000 - \$19,999	95	47	18	14	21
\$10,000 - \$14,999	95	44	19	10	27
\$ 7,000 - \$ 9,999	91	37	28	11	24
\$ 5,000 - \$ 6,999	90	28	23	17	32
\$ 3,000 - \$ 4,999	85	19	15	29	37
Under \$3,000	89	14	12	24	50
POLITICS					
Republican	93	42	24	14	20
Democrat	92	42	17	14	27
Independent	96	43	20	16	21
RELIGION					
Protestant	93	42	20	12	26
Catholic	95	41	18	18	23
OCCUPATION					
Professional & Business	98	56	20	11	13
Clerical & Sales	93	47	18	20	15
Manual Workers	93	40	20	15	25
Non-Labor Force	90	24	18	19	39
CITY SIZE					
1,000,000 & over	95	43	18	17	22
500,000 - 999,999	98	47	21	13	19
50,000 - 499,999	95	40	18	16	26
2,500 - 49,999	94	42	22	13	23
Under 2,500, Rural	88	41	19	13	27
Favor procedure	97	51	18	14	17
Oppose procedure	91	26	25	18	31
Would have operation	97	52	19	13	16
Would not have operation	90	29	22	17	32

## FAVOR/OPPOSE "TEST TUBE BABY" OPERATION

**Question:** (Asked of the total sample.) "Actually, what the doctor did was to remove an egg from one of the woman's ovaries and fertilize it in the laboratory with sperm from her husband. The embryo was then implanted in her uterus. The embryo grew inside the woman and was born like other babies. Some people oppose this kind of operation because they feel it is 'not natural'. Other people favor it because it would allow a husband and wife to have a child when otherwise it would be impossible. Which point of view comes closer to your own?"

August 4 - 7, 1978

	Favor operation	Oppose operation	No opinion
<b>NATIONAL</b>	<b>60%</b>	<b>27%</b>	<b>13%</b>
<b>SEX</b>			
Male	59	26	15
Female	61	29	10
<b>RACE</b>			
White	62	26	12
Non-White	39	41	20
<b>EDUCATION</b>			
College	74	18	8
High School	61	26	13
Grade School	30	51	19
<b>REGION</b>			
East	62	29	9
Midwest	56	27	17
South	55	30	15
West	70	22	8
<b>AGE</b>			
Total under 30	71	21	8
18 - 24 years	69	23	8
25 - 29 years	74	19	7
30 - 49 years	65	23	12
50 & older	47	36	17
<b>INCOME</b>			
\$20,000 & over	71	19	10
\$15,000 - \$19,999	64	24	12
\$10,000 - \$14,999	61	25	14
\$ 7,000 - \$ 9,999	52	34	14
\$ 5,000 - \$ 6,999	50	38	12
\$ 3,000 - \$ 4,999	45	39	16
Under \$3,000	38	45	17
<b>POLITICS</b>			
Republican	60	27	13
Democrat	58	30	12
Independent	66	22	12
<b>RELIGION</b>			
Protestant	61	26	13
Catholic	56	32	12
<b>OCCUPATION</b>			
Professional & Business	73	18	9
Clerical & Sales	67	26	7
Manual Workers	58	28	14
Non-Labor Force	46	39	15
<b>CITY SIZE</b>			
1,000,000 & over	61	27	12
500,000 - 999,999	61	26	13
50,000 - 499,999	61	30	9
2,500 - 49,999	57	30	13
Under 2,500, Rural	59	25	16
<b>Parents</b>	<b>66</b>	<b>23</b>	<b>11</b>
<b>Non-parents</b>	<b>54</b>	<b>31</b>	<b>15</b>
<b>Would have operation</b>	<b>93</b>	<b>3</b>	<b>4</b>
<b>Would not have operation</b>	<b>18</b>	<b>69</b>	<b>13</b>
<b>Church attenders</b>	<b>51</b>	<b>35</b>	<b>14</b>
<b>Non-church attenders</b>	<b>65</b>	<b>23</b>	<b>12</b>
<b>Can explain operation</b>	<b>75</b>	<b>17</b>	<b>8</b>
<b>Can't explain operation</b>	<b>53</b>	<b>34</b>	<b>13</b>

# WILLINGNESS TO HAVE "TEST TUBE BABY" OPERATION

Question: (Asked of the total sample.) "Suppose you were married and wanted to have a child but were unable to do so. Do you think you would or would not be willing to undergo this procedure if it would enable you to have a child, or not?"

August 4 - 7, 1978			
	Would be willing	Would not be willing	Don't know
NATIONAL	53%	36%	11%
SEX			
Male	54	33	13
Female	52	38	10
RACE			
White	55	34	11
Non-White	34	55	11
EDUCATION			
College	69	25	6
High School	53	35	12
Grade School	26	58	16
REGION			
East	54	34	12
Midwest	49	39	12
South	51	38	11
West	63	31	6
AGE			
Total under 30	64	28	8
18 - 24 years	62	29	9
25 - 29 years	65	28	7
30 - 49 years	57	34	9
50 & older	42	43	15
INCOME			
\$20,000 & over	66	28	6
\$15,000 - \$19,999	60	32	8
\$10,000 - \$14,999	49	37	14
\$ 7,000 - \$ 9,999	48	40	12
\$ 5,000 - \$ 6,999	43	41	16
\$ 3,000 - \$ 4,999	35	54	11
Under \$3,000	39	45	16
POLITICS			
Republican	53	37	10
Democrat	52	38	10
Independent	58	31	11
RELIGION			
Protestant	53	37	10
Catholic	50	39	11
OCCUPATION			
Professional & Business	67	26	7
Clerical & Sales	55	27	18
Manual Workers	52	38	10
Non-Labor Force	37	48	15
CITY SIZE			
1,000,000 & over	53	33	14
500,000 - 999,999	55	38	7
50,000 - 499,999	53	37	10
2,500 - 49,999	50	41	9
Under 2,500, Rural	55	33	12
Parents	57	34	9
Non-parents	49	37	14
Favor procedure	83	11	6
Oppose procedure	6	90	4
Church attenders	44	44	12
Non-church attenders	59	31	10
Can explain operation	68	24	8
Can't explain operation	46	43	11



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A STUDY OF THE ATTITUDES OF AMERICAN WOMEN TOWARD  
THE "TEST-TUBE" PROCEDURE AND RELATED MATTERS

SUMMARY SECTION

BY

LOUIS HARRIS AND ASSOCIATES

AUGUST, 1978

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## SUMMARY

### 1. Introduction

Fifteen hundred and one (1501) randomly selected adult American women were interviewed about their attitudes toward the "test-tube" procedure of producing a baby and toward related matters. All interviews were conducted from centralized phone banks in New York City, by experienced female interviewers on August 4th, 5th and 6th, 1978.

### 2. American Women Give the Procedure Qualified Approval

#### 2.1 Major Conclusions

The data reveal widespread sympathy for the married couple who want children but are unable to conceive naturally. The "test-tube" procedure receives most support when it is employed, after scientific testing, as a last resort for married couples using their own sperm and eggs. Although the women, by 42% to 16%, would prefer that such a couple adopt a child, it is important to note that 16% would prefer the "test-tube" procedure and 24% say it would not matter which method were used.

## 2.2 Other Findings

More than a majority of American women (52%) approve of the "test-tube" procedure whereby Leslie Brown recently gave birth in England. Although nearly one-quarter (24%) of the women disapprove of the procedure and an equal amount (24%) are unsure, a substantial 85% believe the procedure should be available to married couples who are otherwise unable to have children. This 85% contrasts sharply with:

- the 22% who believe it should be available to single women who are unable to have children;
- the 21% who believe it should be available to unmarried couples who are living together and who are unable to have children;
- the 12% who believe it should be available to single women even if they can have children; and
- the 11% who believe it should be available to lesbians or homosexuals.

Additional qualifications to approval are suggested by:

- the 63% who would prohibit using the "test-tube" procedure until further testing determines its impact upon birth defects vs. the 24% who want it to be available now (8% are not sure and 5% believe the procedure should never be available);
- the 75% who would allow use of the procedure only if all other methods to precipitate childbirth have failed vs. the 12% who would allow use of the procedure even if all other methods had not yet been attempted (10% are not sure and 3% believe the procedure should never be administered); and



-- the 50% who oppose using federal money to further research into "test-tube" babies vs. the 42% who favor this use of federal funds (8% are not sure).

A plurality of women (49%) believe a married couple should be allowed to use the sperm of another medically-approved man when the husband is unable to provide healthy sperm. Forty percent (40%) say this should not be allowed and 10% are unsure.

A plurality (45%) would allow doctors to remove more than one egg from a woman, fertilize them all and discard all but the one to be inserted for development, while 40% would not allow this and 14% are not sure. Disapproval of the procedure of discarding is especially pronounced among Catholics: 39% say doctors should be allowed to do this while 48% say doctors should not be allowed to do this (12% are not sure).

### 3. American Women Are Divided About Their Personal Use of the "Test-tube" Procedure

#### 3.1 Major Conclusions

Although a plurality of women (48%) would consider personally using the "test-tube" procedure if they were unable to have a baby (44% would not consider it and 7% are unsure), adoption remains the leading alternative when natural childbirth is difficult or impossible (57% endorse it as the preferred personal alternative). Yet, more than one

out of every five American women (21%) would prefer undergoing the "test-tube" procedure under these circumstances and 16% say the particular method utilized would not matter to them (6% are unsure). That the "test-tube" procedure is the choice of 21% of the women, and that 48% would consider using the procedure themselves, is remarkable in light of its very recent emergence as an alternative.

### 3.2 Other Findings

We have seen that a plurality of American women (49%) believe a married couple should be allowed to use the sperm of another medically-approved man in the event the husband is unable to provide healthy sperm. Only 22% of the women would actually consider using the sperm of someone other than their mate under these circumstances, while 72% would not consider it and 6% are unsure. Over two-thirds (69%) would not want to pick out their baby's characteristics before he or she were born, but over one-quarter (27%) would want to make such a selection (3% are not sure). Of those who would want to pick out the characteristics of their baby before he or she were born, 62% would not want to do this if it entailed using the sperm or eggs of someone other than themselves or their mate, while over one-quarter (28%) would want to do this even if it did entail using the sperm and eggs of others (10% are not sure).

4. More Than One In Four American Women Have Experienced Some Sort of Trouble Having A Baby

4.1 Major Conclusions

Twenty percent (20%) of adult American women have tried to get pregnant for a full year but could not and 16% have been told by a doctor that they would have trouble having a baby. This yields a total of 28% (some women answered "yes" to both of the above questions) of adult American women who have experienced, are experiencing or will experience some kind of difficulty in having a baby.

4.2 Other Findings

Of those women experiencing some difficulty, 25% have been told they are unable to have a baby (7% of the total sample) and 61% say this difficulty is due to their own, rather than their mate's problem. Ten percent (10%) of these women have considered using artificial insemination.

5. Women Who Plan To Have Children In The Future Are More In Favor of The "Test-tube" Procedure Than Are Others

5.1 Major Conclusions

Two-thirds (66%) of those women planning to have children in the future (22% of the total sample) approve of the "test-tube" procedure and 62% would consider undergoing the procedure personally. These figures are

significantly higher than the 52% of all women who approve of this procedure and the 48% who would consider using it themselves. In addition, three-quarters (75%) of women who approve of the procedure would consider using it personally. Women who are most likely to use the procedure -- those who have experienced trouble having a baby due to their own problem or difficulty -- are also among the strongest supporters: 61% approve, 21% disapprove and 17% are unsure. A relatively large 55% of this group would consider using the procedure themselves. Disproportionate support for the procedure is also found within younger women (under 30); another group which is among the likeliest future child-rearers. In fact, the percentages of those approving of the procedure actually decreases from the youngest to the oldest age group, with the middle-aged placed mid-way along this continuum:

Table 1

APPROVAL OR DISAPPROVAL  
OF THE "TEST-TUBE" PROCEDURE  
(Questions 2 and 3)

	-----AGE-----		
	Under 30 (397)	30-49 (548)	50 and over (553)
	%	%	%
Approve	65	54	40
Disapprove	17	21	32
Not sure	18	25	27
Refused	1	1	-



## 5.2 Other Findings

Disproportionate percentages of the following groups approve of the "test-tube" procedure:

- women with at least a four-year college education (72%);
- women who have had an abortion (68%);
- liberals (66%);
- women who favor legalized abortion (64%);
- professional or managerial women (64%);
- Westerners (63%);
- women with household incomes of more than \$20,000 per year (60%);
- women with household incomes of \$10,000-\$20,000 per year (56%); and
- women with some college or technical school education (55%).

## 6. Reasons Behind The Attitudes

Women who approve of the "test-tube" procedure do so because it is beneficial for those who want children (61%), because it provides an alternative (31%), because the couple should have the choice (11%) or because they relate to it personally (5%).\* Disapproval stems from feelings that the procedure is unnatural (47%), from moral or religious reasons (30%) or from fears of the dangers or risks involved.

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\* These are categories of responses to open-ended questions and not verbatim replies. For a more detailed description of the responses, see questions 4, 5 and 8 on the printout or request the questionnaires to obtain the verbatims.

## 7. Technical Note

This study involves interviews with 1501 randomly selected adult (18 or older) women who live within the United States (excluding Alaska and Hawaii). All interviews were conducted by experienced female interviewers from centralized phone banks in New York City between August 4th and 6th, 1978. Each interviewer was monitored at least once per interviewing session in order to prevent and correct any errors. The sample was stratified along two dimensions: geographic location and metropolitan (or non-metropolitan) status. Ultimate clusters were included in the sample according to their contribution to the total adult population. Respondents were chosen by a form of random digit dialing. The area codes and first five digits of telephone numbers were used to locate respondents in ultimate clusters. The final two digits were randomly varied in order to include the population of unlisted numbers in the sample frame.

As in any survey of this type, percentages obtained from the sample will differ slightly from those which would have been obtained had the entire population of adult American women been surveyed. The sampling error for percentages based upon total respondents (1501) is no more than plus or minus 3%. In other words, the

percentages obtained in the survey should represent those of all adult American women plus or minus approximately 3%. The sampling error for percentages based upon subgroups of the sample will be somewhat higher.





PUBLIC AWARENESS AND GOVERNMENT REGULATION OF RESEARCH  
ON IN VITRO FERTILIZATION IN HUMANS

Bernard Barber, Ph.D.



Members of the Ethics Advisory Board:

Thank you for the privilege of making a statement that I hope will be of help to you in your present deliberations about whether to lift the existing moratorium on in vitro fertilization research in humans. I realize that you have a narrow and specific goal in your deliberations, that of coming to a decision, aye or nay, on this matter. Yet I know from Secretary Califano's charge to you that you have broader concerns for some ethical and social aspects of this problem that may not be narrowly related to your decision, but are certainly more generally and indirectly related to it. I would like to address myself to two of these larger, contextual concerns: one has to do with the problem of public knowledge and involvement with the issue of in vitro fertilization; the other has to do with the problems of professional, public and governmental regulation of research in this field and in related fields of biological discovery and innovation.

First, then, the matter of public knowledge and involvement. The work on in vitro fertilization of human ova, with a view to eventual implantation and maturation, by Patrick Steptoe and R.G. Edwards was begun about ten years ago and became known almost immediately to various members of the scientific and bioethics communities. Edwards took the lead

in presenting the work he was doing with Steptoe to various scientific and ethical conferences and to the reading publics of such distinguished journals as Nature. Comments, more negative than positive, on Edwards' work and writing were made as early as 1971 by Leon Kass in the New England Journal of Medicine and by Paul Ramsey in the Journal of the American Medical Association, accompanied in the case of the latter by an editorial comment taking a stand against further work on in vitro fertilization in humans. I was myself a part of this early effort by professionals to attend to the Steptoe and Edwards work. In 1973, in my capacity as bioethics consultant to the Population Office of the Ford Foundation, which had given funds to Edwards in the hope that he might contribute valuable knowledge for its extensive program of grants for research in reproductive biology, I visited Edwards in his laboratory at Cambridge. I spent the better part of the day talking with him and satisfied myself that he was aware of the ethical problems arising from his work and that he and Steptoe were following what were then the standard procedures, and more, for evaluating risk/benefit ratios for their patient-subjects and for getting informed consent not only from the potential mothers but from their husbands as well. I should add that a member of the staff of the Population Office of the Foundation made a parallel investigation and, based on a more professional knowledge of



biology than mine, came to the same conclusion. Soon thereafter, the Ford Foundation ended its funding for Edwards, not on ethical grounds, but because its panel of scientific advisors for the reproductive biology grants came to the conclusion that there were other more promising lines of research for the advance of knowledge in that field.

This early flurry of scientific and professional concern with the ethical problems of human in vitro fertilization did little to raise the level of general public consciousness in this area. The concern remained limited to small and knowledgeable elites. Even the Hastings Center Report, a journal/newsletter which so very usefully mediates between the professional and general publics on a wide range of bioethical problems, has had no articles on human in vitro fertilization in all the eight years it has been published, from 1970-1978. I should add, of course, that the members of the Hastings Institute staff were well aware of the Kass and Ramsey articles that appeared elsewhere in the early 1970's. And I should further add that the fall, 1978, issue of the Hastings Center Report will contain several articles on in vitro fertilization.

Public awareness and lack of involvement with in vitro fertilization in humans was dramatically ended, of course, with the announcement of the impending birth of Baby (Louise) Brown, Steptoe and Edwards' first success. The rather remark-

able coincidence of the Del Zio suit against the College of Physicians and Surgeons at Columbia University and Dr. Raymond Van der Wiele for alleged wrong-doing in an abortive attempt at in vitro fertilization only heightened the already enormous public interest. Both of these events cannot but work to change the whole social and political atmosphere in which your deliberations are taking place. Your final statement will be speaking not just to some small "attentive publics" of scientists and bioethics professionals but to large parts of the whole American public. For a society with values like ours, this has to be a good thing. We need the knowledgeable awareness of the public not only on value grounds but because such awareness is necessary for the public's own instrumental welfare, to protect itself and to achieve its own individual and collective goals. I am not now, most certainly, advocating decisions in such complex matters as you are deliberating by the public alone, with a disregard of expert and knowledgeable advice. We need, and you are getting, a considerable supply of expertise from scientific, ethical, and social and political authorities. Their statements have to be taken with the views of, and broadcast back to, the general public whose knowledge and concern are now involved.

I am saying, I suppose, that we should not deplore, as those of us who are more knowledgeable about these matters

sometimes tend to do, the birth<sup>o</sup> of Baby Brown and the Del Zio case as "mere media events" which cater only to ignorance and sensationalism. Dramatic events of this kind, especially because they are cast in all the imagery of Huxleyan social control and test-tube babies (even though the test tubes are really petri dishes) are enormously educational. We may regret that public consciousness has to be stirred by sensation and scandal, but that seems to be one of the effective ways in which widespread public attention, with all the demands on it that exist, is won. For better or worse, some notable reforms have been made possible by public scandal. Consider only the passage of the Kefauver-Harris Drug Amendments in 1952 because of the thalidomide scandal or the passage of the legislation for the National Commission for the Protection of Human Subjects because of the 'Tuskegee scandal in 1973. Indeed, the whole history of improvements in food and drug legislation in this country might be written in terms of the energizing and mobilizing effects of public awareness as a result of public scandal.

In neither the Tuskegee nor thalidomide cases, nor probably in any case, are scandal and public sensation enough. We need all the expert knowledge, the forecasting, the early warning systems we can get. Public consciousness and concern aroused through sensational media events can then be focused

and wisely guided by available expertise. Fortunately, in the area of bioethics, as in many related fields of biological consequence and concern, we now have an active and competent community of specialists, with their own institutes, journals, encyclopedias, forums, and larger public and political audiences. This community can provide the early warning system we need before sensational events occur and can then provide some of the knowledge and wisdom that is necessary afterwards. As you well know, this community does not necessarily make decisions like yours easy, but they probably do make the matter easier than it would otherwise be. Policy advisors like this board can take advantage of public awareness, stimulated by sensation, to base judgements both on lay expressions of values, for example in editorials, news stories, public opinion polls, and on the expertise of the biological scientists and ethicists. This is desirable in a society that values expertise and popular opinion.

Just since the second world war there has been a considerable shift in the general expectation that the public will in some way be involved in the discussion of new social problems brought about by scientific advances. I can testify to this on the basis of my own experience in writing about what the social responsibilities of science should be. When I published my book, Science and the Social Order in 1952 (Free Press, now reprinted, Greenwood Press, 1978), I had a chapter called "The Social Control of Science," in which



the matter of what the social responsibilities of scientists were was analyzed. That chapter had as its substantive examples, of course, given the problems of the time, atomic arms and atomic energy. And a basic assumption of the chapter was that the changing social responsibilities of science in the atomic energy and arms fields would be worked out between interacting elites from the government and from science. There was no mention of the public as a factor in these responsibilities and decisions. Twenty-five years later, when we look at the discussions of problems caused by advances in medicine and biology, problems such as you are dealing with for in vitro fertilization or problems connected with DNA or new therapeutic drugs, there is nearly universal and continuing reference to the involvement of the public and its representatives. This very Board is scrupulous in not only holding hearings open to the public, both organized and unorganized, but in advertising such hearings widely through letters, the newspapers, and the radio and T.V. media. The public feels free to come and state its views. You, and everyone else who makes decisions for the public welfare in matters connected with advance in science and medicine, are expected, not as a matter of convenience but on moral and political grounds, to hear from the public.

I turn now to my second topic, the problems of professional, public and governmental regulation of biological research such as in vitro fertilization in humans. Having reviewed the major fears expressed by those who oppose research in this area, e.g., fears that Baby Brown (and other such children) will be damaged by being so public and visible a person; that this is a step toward a womb-free Huxleyan Brave New World; that surrogate mothers will now offer their wombs for hire; that we will have egg banks, just as we now have sperm banks, for "mere" commercial contracts and financial payments; that we will have gene splicing and the production of clones and chimera; and that there will no longer be any poetry, any surprise in having a baby; and having also viewed the major reassurances against these fears expressed by those who would have you vote aye to lifting the moratorium on in vitro research, e.g., the reassurance that this is a therapeutic procedure; that it offers no excessive risks to implanted mothers; that there is no excessive risk of deformed babies; that this research is no more in need of special evaluation than other therapeutic innovations about which some measure of uncertainty prevails, such as coronary bypass surgery; that we should not succumb to "slippery slope" arguments

about the evils scientists will commit next if this is permitted; and that in vitro fertilization is not essentially different ethically from artificial insemination, which is now allowed; having viewed both these fears and these reassurances, I come out once again where I did five years ago with Robert Edwards, for the continuance of research on in vitro fertilization and for research on the therapeutic procedure of implantation where this is accepted by informed and consenting spouses. I am for this work but only on the condition that there be continuous monitoring of present procedures and of possible next steps by such knowledgeable and responsible review bodies as local peer-review boards and national bodies such as you yourselves constitute, and preferably with the two in closer and more effective combination than now exists between the local boards and national agencies. Rules should be established for present research and monitoring necessary not only to ensure compliance with those rules but to discover new problems and possible advances in research which require new scrutiny and new rules.

All of this, of course, will be objected to as unnecessary and undesirable regulation by many researchers, not only in the field of in vitro fertilization but in biological research more generally. Because of the enormous value they place on

their own autonomy, researchers do not welcome what they define as "outside" regulation, even when they themselves do not take the initiative to set up effective self-regulation or when it is clearly the case that the public interest is so large that regulation must consist of a mixture of "inside" and "outside" bodies and rules. Yet our experience with ethical regulation of research during the last ten years or so has been favorable. Thanks to the regulations initiated by the National Institutes of Health in 1966 requiring local peer review for all research using human subjects, the standards and practice for such research today are considerably higher than they were, though the situation is still not entirely satisfactory, as the excellent research by Gray, Tannenbaum and Cooke on local peer review boards well demonstrates. There is no evidence, though fears are sometimes expressed by ideologues, that there has been any significant hindrance from these regulations and from the local peer review boards' decisions to the progress of research. In this same regard, it seems to me that the National Commission for the Protection of the Human Subjects of Biological and Behavioral Research has been a great success. Despite the fears expressed before the Kennedy and Rogers committees when the legislation for the Commission was



being considered, the National Commission's investigations and recommendations, as finally embodied in rules by Secretary, Department of Health, Education and Welfare, have not been harmful to research. And they certainly have been helpful for subjects in general and for subjects who are prisoners, children or mentally retarded in particular. As requested by Congress, these special populations were specifically considered by the Commission. In the case of its recommendations on psychosurgery, a topic also specifically mandated to the Commission by Congress, the Commission may even have had a considerable liberating effect on experimental therapy. Where only wild stories and secretive defenses had existed before, the Commission's objective and expert investigation of psychosurgery cleared the air and showed what was possibly helpful and ethical, what was unethical. Proceeding from the experience of the N.I.H.-D.H.E.W. regulations and the recommendations of the National Commission, researchers can accept regulation such as might come in the recommendations of your Board without any great fear. Indeed, it is my hope that not only will this Board become a permanent advisory body to the regulatory agencies embodied in the Department of Health, Education and Welfare, but that the President's Commission that is now recommended in legislation pending in Congress will also be established. There is plenty of useful work to do.

Part of your larger task, then, must be to persuade the research community that it must not be opposed on principle to regulation of research and that in practice it must join with bodies like this and with local peer review groups to create regulations which will as successfully as possible accommodate to one another the progress of science and the new ethical standards of our society for biomedical research. This task is not an easy one. In an earlier paper, I asserted that, because of the excessive emphasis of researchers on their own autonomy as against the welfare of their subjects, liberalism often stopped at the laboratory door. I asserted that researchers who were in favor of all kinds of social and governmental regulations outside their laboratories were too strongly opposed to it inside. I had a vivid experience of this during my visit with Robert Edwards in 1973, mentioned earlier. Let me read from the report on that visit that I wrote at the time: "On specifics (of the ethical issues involved in his work) there were really no disagreements between us. Only on the very general issue of governmental action was there a wide ideological gulf between us, with Edwards countering every recommendation by me of a governmentally established Commission on the Protection of Human Subjects and every declaration by me that such a

Commission would be the most effective safeguard of biomedical innovation with a flat statement that he was against 'any' governmental action in this area. Apparently this strong individualism and anti-governmentalism runs only to biomedical research, so far as Edwards is concerned. He proudly declares himself 'a socialist' in all other matters and is politically conscientious enough that he serves, as an elected official, on the Cambridge Town Council".

Edwards is not the only researcher, biological or social, for whom a liberal openness to necessary regulation stops sharply at his laboratory door. I hope the final statement of this Board will not only contain a decision to lift the present moratorium on in vitro fertilization research but will prescribe a set of rules for that research in its present and future states that will encourage researchers to open their laboratory doors a little less reluctantly to the necessary rules for fully ethical research.

There is much talk nowadays among scientists about governmental and public restrictions on science, and certainly about the increasing danger of such restrictions in the future. A recent issue of Daedalus, one of our most distinguished journals of elite university and intellectual opinion, is entitled The Limits of Inquiry. The articles in this issue were the result of a seminar sponsored and parti-

pated in by a group of powerful and renowned scientists from Harvard, Massachusetts Institute of Technology, and related universities. The burden of this issue is the complaint against present and possible restrictions on scientific work. But what looks like the limits of inquiry to scientists may look like the enlargement of public values to non-scientist members of our national community. And when some of these scientists allege that there is a new and larger "pessimism" about modern science and its consequences, that "pessimism" may seem to be greater "realism" not only to non-scientists in our society but even to a minority among the scientists themselves. There is no need for confrontation between these two points of view, no inevitable zero-sum situation in which everything that is called a regulation of science has to be some vital restriction on science. There is plenty of room for accommodation between the two sets of values, the two points of view. We have seen a great deal of that accommodation already, and we can create more of it. Such constructive accommodation will require much effort and good will from both the scientists and the non-scientist public. Negativism, conservatism, inactivity, following the old paths, old interests, and old values will not do for the considerable and continuing changes we face as a result of the unending and consequential advances of science.



How shall we achieve more constructive accomodation and genuine social change of the social mechanisms for continuing such constructive accomodation in the long run? Fortunately , a variety of change agents have already appeared and been effective. We can learn from the experience of our past and strengthen these change agents. Whatever its diverse and interrelated causes, social change in any area is not embodied in wholly impersonal mechanisms but operates through the actions of a variety of individuals who serve as agents of change. In the area of medical ethics, these change agents have been some insider medical professionals, a miscellaneous set of "humanists" or "bioethicists," some social scientists who have done policy-relevant research, and some people from government.

Insider change agents have been people like the late Professor Henry Beecher of the Harvard Medical School, whose 1966 article in the New England Journal of Medicine describing some 25 articles in the professional medical and research journals that showed evidence of unethical use of human subjects, stunned his colleagues into an awareness of the problem. Unfortunately while Beecher raised the level of consciousness of the medical research world, his analysis was too individualistic, too psychologistic. He thought he was dealing with just "bad guys." What others have pointed out is that it was a "bad system" that was turning "good guys" into "bad guys."

Another important set of insider

professional change agents has been an anonymous group of researchers and administrators at the National Institutes of Health (N.I.H.) who, since the early 1960s, have labored to construct effective regulations for local peer review of the ethical aspects of all biomedical research funded by them. Their great achievement has been creation of the 1966 N.I.H. regulations. Without Beecher and the N.I.H. professionals, recent changes in the medical ethics of human experimentation would have been less effective and less speedy. In other areas of change in medical ethics, such as problems of abortion, genetic counseling, and humane death, insider professionals have been equally important.

But insiders, as we have already suggested, have been more resistant than receptive to these changes. Change would not have occurred without the set of outside change agents from the fields of ethics, philosophy, the law, and the humanities, who have all come to be known, inclusively, as "bioethicists." These change agents have held conferences, written books and papers, given lectures, held seminars, and provided training facilities for all those newly interested in medical ethics and even established specialized institutes to consider its problems. The leading institutions investigating medical ethics are the Kennedy Institute of Bio-Ethics at Georgetown University and the Hastings Institute, a private enterprise

headed by Daniel Callahan and Willard

Gaylin, a psychiatrist-turned-social-critic and moralist.

The bioethicists have come from those fields where a general professional concern for moral values is important. Their involvement with medical ethics is only the latest, and certainly not the last, of the expressions of their general moral concern.

Another set of outsiders has been the professional social scientist such as Diana Crane and Bradford Gray, who have carried out careful research on problems, such as human experimentation and the treatment of dying patients, and who have been much concerned for formulating better medical ethics and better social policy on the basis of the knowledge acquired in their research. These outsiders have felt that the availability of essential facts is indispensable for the rational processes of change to affect medical ethics. The kind of abstract, unspecified, and unsupported statements, which are often forthcoming both from the outsider bioethicists and from the insider professionals are not adequate for successful change in ethics and policy.

Finally, some government people have been important change agents. Senator Javits of New York was responsible for inserting the ethical review clauses into the Kefauver-Harris Drug Amendments of 1962. Senator Edward Kennedy of Massa-

chusetts and his aids and advisors have had a long-standing, continuing, and key influence on the legislation for improving medical thics, especially in connection with the legislation in 1975 for setting up the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, an agency which has provided an excellent model of how new regulations for medical ethics may be constructed with due regard to all the values and interests involved. Beyond congressmen, of course, there has been the important influence, referred to above, of the medical researchers working for the government in the National Institutes of Health. The combination of their professional concerns and the power of the National Institutes, as government-funding agencies, has made their effects on change extensive and beneficent indeed.

Important social change, such as is now occurring in medical ethics, does not proceed along a single path but through multiple and diverse modalities. One such modality is what sociologists call a "social movement." A social movement consists of a diverse, often diffuse (partly organized, partly not) aggregation of people and forces that push toward some new social goal. It is often more effective in raising a moral cry than in defining specific ways of achieving its goal, more successful in raising the



level of social consciousness in the public domain about some new social evil than in carrying through the actual process of reform. The various people and forces pushing for change in medical ethics have something of this character of a social movement. Their diverse, diffuse, overlapping, somewhat conflicting energies are necessary for the birth of the idea of reform, but they are not enough. Moral change has to be supported, established, supplemented, and sometimes led by governmental and legal action.

Governmental and legal action is the other important change modality which has been so significant in causing important changes in medical ethics. But such action, if entirely unsupported by a strong moral base, would be ineffective; it can lead morality a little bit but can never get too far ahead of it. In the case of medical ethics, fortunately, the moral changes created by a social movement have been successfully implemented by a great variety of governmental and legal changes in many different areas of medical ethics. Since the relationship between social movements and governmental and legal actions, between morality and law, are of great consequence in all areas of social change, a close study of what has happened in the area of medical ethics should be instructive for those interested in change in other areas of society.



LIST OF RELEVANT WORKS BY BERNARD BARBER

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STATEMENT TO THE DHEW ETHICS ADVISORY BOARD

Clifford Grobstein, Ph.D.



Statement by Clifford Grobstein to the DHEW Ethics Advisory Board

September 15, 1978

Drs. Biggers and Walters have provided sound appraisals of the scientific background and the ethical issues raised by the matter before you. Dr. Biggers has confined himself entirely to human fertilization in vitro, followed by reimplantation of the product into the female member of an established heterosexual couple who supplied the gametes. Dr. Walters has dealt with broader possibilities in the immediate and longer term future.

By way of critique, I take exception to nothing they have said. I do, however, view the matter from a different perspective that leads to somewhat different emphases. My perspective is that of the requirements for effective policy in a consequential area of substantive uncertainty and normative conflict. In such an area not only are scientific fact and ethical considerations relevant but so, too, are the general state of public opinion, the interests of special publics, and the practical feasibility of implementing various policy options. In our society, moreover, even sound policy cannot long frustrate strong motivations within the body politic.

In this content, I offer the following additional thoughts:

1. It is not within the capability of this agency, or any other U.S. agency, to control advancing world knowledge or its application to human purposes.

The birth of Louise Brown in England, while a de facto moratorium on the research that made her birth possible existed in the U.S., underscores the fact that research

is international in origins and effects. Yet, though our impact is thus limited, we cannot maintain a head-in-the-sand posture. We must have a sound and flexible policy that accords with changing realities.

2. Though Dr. Walters has dealt broadly with the ethical issues involved in an entire area of research, it is not the case that all possible advances are equally imminent. Dr. Biggers has correctly focused on the most immediate issues and Dr. Walters has equally correctly noted that there is a logical and scientific progression from the more to the less immediate issues, and that this calls for a more comprehensive focus than the end of our nose. Appropriate policy may include phased decision-points that allow us to take growing experience into account.
3. Actually, we are not starting from scratch, certain relevant decisions already have been made. There is a general consensus, for example, that no one may claim the unlimited right to experiment on human beings. The protection of essential human rights and the dictates of general social policy must be taken into account. The central conceptual and ethical problem that we face in this connection is the boundary of application of the term "human being". Dr. Walters has illustrated the problem and it seems clear that no full consensus was reached -- or awaited -- before Louise Brown was born.



Interestingly, this case avoided many of the more knotty, down-the-road issues and engendered more curiosity and notoriety than moral outrage. To some it may seem another example of the camel getting its nose under the tent, to others it illustrates a process of consensus "at the margins" of a complex issue too difficult to cope with as a whole.

4. For example, at the margin, neither the law nor any responsible person would exclude viable new-born infants from the category of human beings even though they are not yet fully independent and do not yet display full human cognitive behavior. On the other hand, very few persons would regard immature oocytes, or even mature sperm, as human beings although both are clearly human in certain properties. It is in the range of mature oocytes to birth that consensus breaks down.
5. At some stage in the developmental continuum between mature oocyte and birth, a human being emerges who commands the full protection of human rights. However, consensus currently is lacking as to the particular stage and the essential characteristics that define it. Indeed, the specific time may not be the same for all purposes, just as the moment of death may not be best defined in the same way for all purposes.

6. It is scientifically defensible that a central aspect of the critical emergent stage is the rise of what we may call sentient awareness. This state is not, at the present time, definable objectively. Nonetheless, there is ethical consensus that scientific investigation must not intrude harmfully or cruelly upon it. Moreover, there is scientific consensus that sentient awareness depends upon maturation and function of the nervous system. The brain is especially involved and the state probably arises gradually during brain maturation.
7. Although we do not know whether an isolated brain can display the critical state the evidence is strongly against its existence in other cells, tissues or organs that are not functionally connected to the brain. Stated another way, sentient awareness arises in a whole developing fetus and not in isolated parts, with the possible exception of the brain. These are important considerations in deciding when and how to extend the blanket of human rights to the human fetus and its parts.
8. Moreover, there is a fair consensus that human beings, for various reasons especially including ethical ones, are not optimal subjects for experimental genetic or developmental studies. There are strong grounds, therefore, to restrict their use severely unless all other alternatives have been fully explored or unless the

question to be asked is specific to human beings.

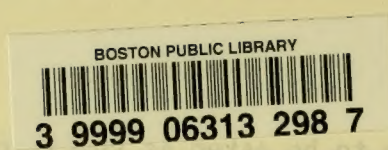
This approach is now incorporated into regulation of the use of human subjects, including fetuses.

9. The argument does not equally apply to cells, tissues or organs that have no reasonable prospect of possessing or developing sentient awareness. These are human materials rather than human beings and there are established practices for dealing with and disposing of them. They should be available for responsible experimental use under conditions that assure:
  - a) substantial benefit to individual or social welfare,
  - and b) absence of substantial harm to the donor source or other involved persons.
10. Substantial benefit may stem from:
  - a) application of knowledge gained on other species to the human species in order to achieve widely accepted human purposes;
  - b) increased understanding of processes that are unique in degree or kind to the human species, e.g. mechanisms of cognition.

These considerations have implications for sound public policy:

1. In the general area of experimentation on and with human embryos a mechanism such as this Board is desirable to





facilitate interaction between involved scientists and persons with other significant expert and public perspectives.

2. Stemming from this interactive consideration of research directions guidelines should be formulated that are addressed to particular issues as they arise. Public input to the guidelines should be encouraged. Applicability of the guidelines should be extended as widely as possible in the U.S. and abroad.
3. The guidelines should relax restrictions at the margin of the complex of issues involved and, as consensus develops, relaxation should extend centrally as far as reasonable consensus exists.
4. As examples, studies in vitro of human fertilization and development of whole embryos to but not beyond the implant stage should now be encouraged for appropriate purposes and under specified conditions with respect to termination of development and disposal of human materials. Similarly, appropriate studies in vitro of human cells, tissues and organ rudiments (partial ectogenesis) should be encouraged where there is no possibility of the appearance of sentient awareness. Cloning, genetic intervention and cell fusion experiments that might yield sentient human or humanoid beings should be discouraged pending further scientific experience and fuller ethical, social and political assessment.





